**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**PUBLIC HEALTH SERVICE**
**FOOD AND DRUG ADMINISTRATION**

# ORTHOPAEDICS AND REHABILITATION DEVICES ADVISORY PANEL MEETING

**December 12, 1997**

**Bethesda Holiday Inn**
**Versailles Ballrooms III and IV**
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Dr. Casey Kerrigan
Dr. David B. Hackney
Dr. Joseph E. Hale
Dr. Janine E. Janosky
Dr. Cato Laurencin
Dr. Harold Wilkinson
Dr. Michael Yaszemski
Dr. Doris S. Holeman, Consumer Representative
Ms. Cindy Domecus, Industry Representative

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Dr. Raymond Silkaitis
Dr. John A. Todhunter
Dr. Jeffrey S. Ross
Dr. Russell Hardy
Dr. Donald Johnson
Dr. Derrick McKinley
Dr. Francois Porchet
Dr. David Spencer
Dr. James Anderson
Dr. Phillip Lavin

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P R O C E E D I N G S (9:07 a.m.)

MS. NASHMAN: The conflict of interest statement. The following announcement addresses conflict of interest issues associated with this meeting, and is made part of the record to preclude even the appearance of an impropriety.

The conflict of interest statutes prohibit special government employees from participating that could affect their or their employer's financial interests. To determine if any conflict existed, the agency reviewed the submitted agenda and all financial interested reported by the committee participants. It was determined that no conflicts existed.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him- or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

The appointment to temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, and as amended April 20, 1995, I appoint the following people as voting members of the Orthopaedics and Rehabilitation Devices Panel for the duration of the meeting on December 11 and 12, 1997: Cato T. Laurencin; Michael J. Yaszemski; Edward Y. Cheng; Leon J. Wobler, who has already left the meeting for the day; Joseph E. Hale; Janine Janosky; D. Casey Kerrigan; and Harold Wilkinson. Additionally, I appoint the following people as voting members of the Orthopaedics and Rehabilitation Devices Panel for December 12, 1997: Thomas W. Bauer and David Hackney.

For the record, these people are special government employees, and are either a consultant to this panel, or a consultant or a voting member of another panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review. They have reviewed the material to be considered at this meeting.

Also because the position of panel chairman for the Orthopaedics and Rehabilitation Devices Panel is current vacant, I appoint Barbara D. Boyan to act as temporary chairman for the duration of the Orthopaedics and Rehabilitation Devices meeting on December 11 and 12. For

the record, Dr. Boyan is a special government employee as a voting member of the Orthopaedics and Rehabilitation Devices Panel. Dr. Boyan has undergone the customary conflict of interest review, and she has reviewed the material to be considered at this meeting.

This is signed D. Bruce Burlington, Director for the Center of Devices and Radiological Health, and dated December 4, 1997.

Also for the record, this statement was signed yesterday, and I failed to read that it had been signed.

One more point of interest. The Federal Register notice dated November 25, 1997, stated that there would be a closed session at this meeting between 8:00 a.m. and 9:00 a.m. For the record, that closed session existed only between 8:30 a.m. and 9:00 a.m.

Before getting started, I would like to introduce the panel members who are here helping us today, who we truly appreciate. For my own ease, I'm going to just read the list of panel participants in alphabetical order: Dr. Barbara Boyan, who is a biologist, and also chairperson for this meeting; Dr. Doris Holeman, who is the consumer representative for the meeting; Dr. Cato Laurencin, an orthopaedic surgeon; Dr. Michael Yaszemski, an orthopaedic

surgeon; Dr. Thomas Bauer, a pathologist; Dr. Edward Cheng, an orthopaedic surgeon; Cindy Domescus, who is the industry representative acting for today's portion of the meeting; Dr. David Hackney, a neuroradiologist; Dr. Joseph Hale, a biomechanistician; Dr. Janine Janosky, a biostatistician; Dr. Casey Kerrigan, a physiatrist; and Dr. Harold Wilkinson, a neurologist.

Also at the table is Dr. Celia Witten, the Division Director for the General and Restorative Devices Branches.

DR. WILKINSON: Could I just correct one thing? I'm not a neurologist.

MS. NASHMAN: I'm sorry, a neurosurgeon. I'm very sorry for the discrepancy. I owe you one. I know that is the gravest of insults.

At this point I will turn the meeting over to Dr. Barbara Boyan.

**Agenda Item: Open Public Hearing**

DR. BOYAN: At this time I would like to open the public hearing. At this point, is there anybody in the audience that would like to address the panel on any of the subjects that are for today's session? We ask that all persons addressing the panel come forward.

Okay, looking for a show of hands and not finding any, we will proceed. I would like to introduce Mr. Dillard, who will make a statement to the group.

MR. DILLARD: Good morning, ladies and gentlemen, panel members. I would like to thank you once again for coming and participating today, December 12, for the Othropaedics and Restorative Advisory Committee hearing. On behalf of the Division of General and Restorative Devices, I would like to update the panel and the audience about what has occurred since the last time this panel met.

A couple of changes in the division; we have added quite a few personnel since the last time we got together. We are one of the divisions that is growing, certainly not by leaps and bounds, but by a couple of individuals.

We still are divided into four branches: the Restorative Devices Branch; Marie Schrader is current the branch chief of that branch; Mark Melkerson(?), the Orthopaedics Branch chief. Those are the two branches that this panel actually covers. We also have in the division, the Plastic and Reconstructive Surgery Branch; Steven Rhodes is the branch chief; and the General Surgery Devices Branch, and Dr. George Jan is the branch chief.

Towards the end of this I'm going to tell you

about one of the other very interesting developments that we have had since the last time we got together. We have added one more branch.

One of the other additions of note is Dr. Worly Panich(?), who has been added in the restorative devices area. She is a recent addition as a medical officer. One of the other medical officers is Bob Greenberg in the General Surgical Devices Branch area. He is actual an intern that has joined us very recently, and we are certainly glad to have his efforts also.

We don't anticipate over the next year, to particularly grow. Right now the hiring situation within the agency is pretty much nonexistent. So we are hoping that we can at least keep the current staffing level, and continue to move forward.

At the last panel meeting, if you remember, we met June 9 and 10. You considered three PMAs. They were pre-amendments PMA devices that has been called for PMA under Section 515(b). They were P960053, Advanta Orthopaedics, the Braun Cutting Trapezium Metacarpal Prosthesis; P960054, J and J Professional, the Polydowel(?) Constrain Liner; and P960047 from Osteonics(?) Corporation, the Constrained S-tabular(?) Insert.

All three of these PMAs, after your recommendations and your assistance, your all approved in 180 time frame. It was right about actually 179 or 180 days, so we squeaked in right under the gun. We certainly appreciate your efforts on June 9 and 10.

The interesting piece of information -- actually a couple -- that I wanted to just highlight you to is since we met last time, we have added the Neurology Devices Branch within the Division of General and Restorative Devices. The Neurology Branch was housed in the Division of Cardiovascular, Respiratory and Neurology Devices up until the first part of October.

One of the reasons I think the Neurology Branch shifted was that there were a lot of reviews that were happening between a number of our branches and the Neurology Devices Branch in combination. We thought that we might be able to gain some efficiency in adding it in our division. That seems to be going pretty well, although it was a lot more work I think, than we kind of expected at first.

The other piece of information, and it has been talked about a little bit, and I think you will continue to hear more is the FDA Modernization Act was passed. President Clinton signed it in November. It goes into

effect mid part of February. The FDA Modernization Act has quite a few changes in it, and they are too extensive to actually go through today, but I think by the time we get together next time, we will have that in training, and we might also be able to put something together for an open session to highlight some of the activities that are particularly appropriate for this panel and for our division.

To highlight though, one of the overriding themes in the modernization act is one of cooperation between the FDA and industry. I think you will see on the panel, much more interaction, some that has already begun actually, between FDA personnel and the industry that we regulate. That might also translate into other interactions that you may have with the division in helping us earlier on applications.

With that, if there are any questions, I would be happy to entertain them. If not, I'll turn it back to Dr. Boyan.

DR. BOYAN: Thank you very much, Mr. Dillard.

Are there any other speakers that wish to speak? Since there are no other speakers in this open public hearing, we will now proceed to the open committee

discussion and discussion of the first PMA being presented before the panel today, which is the Premarket Approval Application from Gliatech for ADCON-L Anti-Adhesion Barrier Gel.

I would like to remind the public observers at this meeting that while this portion of the meeting is open to public observation, public attendees may not participate, except at the specific request of the panel.

We are now ready to begin with the sponsor's presentation. I would like to ask that each speaker state his or her name and affiliation to the firm before beginning the presentation. We have allocated one hour to this sponsor presentation.

**Agenda Item: Open Session - Gliatech's ADCON Spinal Anti-Adhesion Barrier Gel - Manufacturer Presentations**

DR. SILKAITIS: Good morning. My name is Raymond Silkatis. I am Vice President of Medical and Regulatory Affairs for Gliatech. I will be providing an introduction, the agenda for our presentation, and introduce each of the speakers before the panel.

On behalf of Gliatech I would like to start the presentation by thanking the Food and Drug Administration

for granting expedited review to this premarket approval application, and especially to the FDA review team for their diligence and hard work during the review process so that we may be here today. We welcome the opportunity to have our premarket approval application considered by the Orthopaedic and Rehabilitation Devices Panel this morning.

To familiarize the panel with the company, Gliatech is a health care company specifically engaged in the research and development of products based on the properties of glial cells for treatment of Alzheimer's disease and cognitive disorders. Gliatech's ADCON technology was derived from our research of glial cells; in particular, glial scar.

From this research, ADCON-L anti-adhesion barrier gel was developed, which acts as a physical barrier to peridural scar and adhesions around nerves around nerves after lumbar surgery procedures.

The product that you see on the left is under review. ADCON-L gel, which contains dextran sulfate, a porcine derived gelatin, and buffered saline is contained in the tube on the lower right. To apply the product to the surgical site, there is a sterile applicator, which is attached to the tube. The packaging that you see there is

the package that is used to distribute the product in Europe and around the world.

As you can recognize, the product is not a spinal implant in the sense that it is to support physical structures, and may remain in the body for years, rather, ADCON-L gel absorbs within four weeks. So ADCON anti-adhesion barrier gel is an absorbable device indicated for use to inhibit post-surgical peridural fibrosis and adhesions, scar, and the resultant clinical sequelae.

We are requesting the panel to recommend this product for approval based on the scientific evidence that we will present to you today.

I would now like to take a few moments to review the agenda. Our program this morning will obviously consist of this introduction. Next there will be an overview of the problem of adhesions and the development of ADCON-L to solve this problem. The clinical relevance of peridural fibrosis will be presented by Dr. David Spencer, Associate Professor of Orthopaedic Surgery at the University of Illinois.

This will be followed by a review of the pre-clinical effectiveness and safety studies that led to the initiation of the clinical studies, and that will be presented by Dr. John Todhunter, Diplomate, American Board

of Toxicology, SRS International.

Now prior to the discussion of the pivotal study, we will review the technique used to evaluate the primary effectiveness variable, and that is scarring, so that the assessment of peridural scar by magnetic resonance imaging will be presented by Dr. Jeffrey Ross, Head, Radiology Research, the Cleveland Clinic Foundation.

Then we will have the results of the pivotal clinical study presented by Dr. Russell Hardy, Professor of Neurosurgery, Case Western Reserve University.

In addition, we have supplemental information. A brief overview of this will be presented by Dr. Derrick McKinley, Medical Director of Gliatech. The supplemental information consists of U.S. study interim results, and that will be presented by Dr. Donald Johnson, Medical Director, Carolina Spine Institute. Further, we have post-study surveillance on the pivotal study, which is longer term data, and that will be presented by Dr. Derrick McKinley.

In addition, we have a surgical video of reoperation cases of patients that have been treated with ADCON and not treated with ADCON. That will presented by Dr. Francois Porchet, Associate of Neurosurgery, Centre Hospitalier, Universitaire Vaudois. Finally, we will have

summary conclusions that will be presented by Dr. Derrick McKinley.

So to begin the presentation, I would like to invite the next speaker this morning, Dr. David Spencer. He is an orthopaedic surgeon at Lutheran General Spine Center, Parkridge, Illinois.

DR. SPENCER: Good morning. I'm Dr. David Spencer. I'm an orthopaedic surgeon from the University of Illinois. I have no financial compensation from the company, however, I do own shares in the company that I purchased privately.

We are talking today about peridural fibrosis, which is a natural consequence of the surgical insult of lumbar disc surgery. Lumbar disc surgery is the gold standard for the treatment of sciatica due to disc herniation. Sciatica due to disc herniation is one of the most commonly performed, and most successful operations that we can perform on the lower back at this time.

It is my contention that scar tissue can affect the neurodynamics of the nerve root by adhesion of the nerve root to the spinal canal, which can adversely affect the outcome, and also complicate reoperation. Peridural fibrosis tethers nerve root dura and complicates any repeat

surgery, making the nerve roots more vulnerable to injury, dural tears, and subsequent arachnoiditis.

In 1983, I published a study that identified the Hoffman ligaments as a mesentery that attaches the normal nerve root into the spinal canal. Hoffman ligaments, by the way, were originally described in 1897, and no clinical significance had been attached to them until we analyzed their relevance to sciatica.

On the right-hand side you can you see a disc herniation that protrudes into the spinal canal and deforms the nerve root. If the nerve root is tethered by Hoffman ligaments, tension is developed in the nerve root; pressure on that nerve root over the apex of the disc herniation produces edema, ischemia, and mechanism of sciatic pain.

The positive straight leg raising test is the most significant clinical indicator of sciatica due to disc herniation, because when the straight leg is raised, tension is applied to the nerve root. If the nerve root is already under tension by virtue of the disc herniation protruding against the nerve root, you have limitation of straight leg raising, and increased pressure on the disc herniation from the mechanism of increased tension.

Obviously, any scar tissue that encompasses the

nerve root can be more tenacious than the Hoffman ligaments in the first place, and therefore, make the nerve root more vulnerable to any deformations of the nerve root by any subsequent disc bulging or disc herniation.

There are just two slides that just depict scar tissue invading the laminotomy defect and surrounding the dural and the nerve root on the level of the hemilaminotomy side. On the right-hand side is the dog specimen that shows the scar tissue in a cross-sectional view.

There has been considerable effort in trying to reduce peridural fibrosis, analyze the scar tissue, and come up with a mechanism to reduce the amount of scar tissue that inevitably forms. In 1983, as I say, I published the Hoffman ligament study. Subsequent to that I did extensive studies on high uranic acid as a bio-absorbable gel to modulate scar tissue. In my opinion, the peridural fibrosis is a potential cause of post-operative pain, and is a significant complication in reoperation, or potential complication in reoperation.

Recently, a study was performed using an MRI scan to evaluate patients with recurrent radicular pain, and there was a correlation between the amount of scar tissue on a post-operative MRI scan, and radicular pain. Most

clinicians are familiar with the scenario where a patient has recurrent or residual sciatic pain in their leg. An MRI scan is obtained. There is no evidence of any residual or recurrent disc herniation, so the report comes back peridural fibrosis and scar tissue.

This is a paper that correlates that finding. Obviously, before MRI scans were available, we had very few means of non-invasively evaluating scar tissue, and therefore, the literature prior to MRI scans does not confirm or refute the scar tissue aspect, because there was no way to non-invasively image it.

Obviously, lumbar laminectomy surgery, being the most common operation in the United States, has a significant impact. If 10 percent of the patients who have an initial laminectomy operation require a subsequent operation at some later date, the effect of the post-operative scar tissue on that percentage of patients is significant.

Previous attempts to modify the scar tissue have provoked lots of efforts at minimally invasive procedures. Microdiscectomy is described as a surgical procedure that tried to minimize the surgical field, but provide the same relief of sciatica by disc herniation removal. Scar tissue

still forms after microdiscectomy surgery.

Chemonucleolysis, percutaneous nucleotomy, laser discectomy -- these are all minimally invasive procedures that were motivated in part to try to find a technique for relieving sciatic pain without an open operative procedure and the associated scar tissue that forms from it. None of those have proved to be as effective as open surgical discectomy, which is still the standard of care.

By the same token, there is no medication that we can give -- steroid, anti-inflammatory medications -- there has been no effective technique that we currently have available to reduce scar tissue following the standard accepted operation.

So in summary, for 15 years I have been looking for a sterile, biodegradable gel that will fill a laminotomy defect following surgery, that would inhibit, to a certain extent, the scar tissue that forms. It would be resorbable, and reduce the amount of permanent scar tissue that was in the patient following the surgery.

So for example, the laminotomy defect, instead of being filled with hematoma and scar tissue, you put ADCON-L on and the ADCON-L permeates the neural canal. It is not just a layer on top, it permeates the neural canal at the

site of the surgery, and hopefully reduces the amount of peridural fibrosis and scar tissue that forms.

On the right is a rat laminectomy model that shows the laminectomy defect of the spinal cord, at two weeks, the scar tissue. With ADCON-L, a minimal amount of scar tissue over the laminectomy defect at two weeks.

So peridural fibrosis is a natural consequence of lumbar disc surgery that can have an affect on some patients following surgery, and has an affect in most patients if you are having to do reoperation on those patients at the level of the surgery.

It is my opinion that if a procedure can be performed that can reduce that scar tissue, then it is a significant advancement in the surgical treatment of sciatica due to disc herniation.

So I'm going to turn over the podium now to Dr. Todhunter, who is going to talk about the pre-clinical effectiveness studies of this absorbable gel.

DR. TODHUNTER: Good morning. I have been asked to briefly review the pre-clinical safety and efficacy data on ADCON-L. I am a consulting toxicologist with SRS International. Gliatech is a client of SRS International, but neither I nor the company have any other financial

involvement with the Gliatech.

A number of pre-clinical safety and efficacy studies were done on ADCON-L prior to its use in clinical trials. These included of course the types of studies that are suggested in the Bluebook Memorandum, as well as rat and rabbit laminectomy studies. The laminectomy studies mimic the intended clinical use of the product, and I believe are the best and most relevant types of studies for evaluating its pre-clinical safety and efficacy. The studies that I'm going to talk about were all conducted in accordance with GLP.

Now the slide on the right lists a number of standard studies recommended for resorbable devices in the Bluebook Memorandum. As can be seen, these particular studies for their particular endpoints gave a reasonably unambiguous safety signal, at least at the pre-clinical level.

Also included the standard Bluebook set are a couple of other studies which were conducted, and in interpreting these particular studies, the laboratory which conducted the studies did not take into account the resorbable nature of ADCON-L, nor for the dermal sensitization study; certain uncontrolled differences in

animal handling and dosing. So as a result, for both of these sets of studies, normal resorption events were reported as irritancy or a sensitizer reactions or possible sensitizer reactions.

In addition, treatment-related, as opposed to substance-related differences confounded the interpretation of the dermal sensitization study.

The results of these studies and the underlying data were reviewed by an outside group of toxicologists, pathologists, and immunologists. I was one of the reviewing toxicologists. The consensus of this independent, third party review was that the findings of the studies were basically due to the process of resorption, as well as treatment differences in the dermal sensitization study, but were not due to irritant or sensitizing properties of ADCON-L.

Now in order to confirm that consensus view, additional studies were designed in cooperation and discussion with the Food and Drug Administration, and they were conducted. One of these was a hypersensitization study which used a better methodology for this particular product, which allowed for good control of treatment differences, and the use of more controls, including a positive control, than

did the original dermal sensitization study. In this study, ADCON-L was not demonstrated to be a sensitizer.

The other study was an acute subcutaneous toxicity study. This study looked at immunological sequelae by micropathology of relevant organs. It also looked of course for what was going on at the implant side, and for systemic toxicity. In this study, there was no evidence of immunological sequelae. There was no systemic toxicity, and there were no adverse tissue reactions seen at the subcutaneous implantation sites.

So in short, when you revisited the issues with appropriately designed and well controlled studies, ADCON-L gives a strong safety signal.

Now this conclusion is reinforced when one looks at the results of the rat and the rabbit laminectomy studies. Now these, as I indicated, are a combination of safety and efficacy studies which mimic the intended human use, and in my opinion, are the most significant and appropriate studies for examining the pre-clinical safety of a product like this one.

These are fairly large studies. There are 128 rats involved; 80 rabbits. They have a long follow-up. It is up to 26 weeks. Now that is about six or seven times

longer than the resorption time of ADCON-L in these studies, which occurs within four weeks.

For both species, one sees normal wound healing, no adverse tissue reactions, and an inhibition of peridural scarring, which is very significant. There are the mean peridural scar scores for rat laminectomy and for rabbit laminectomy. One can see that there is a very strong effect, and it is very high statistical confidence on that.

In closing, I would like to summarize by saying that the pre-clinical data, which we have just looked at, indicate that ADCON-L is safe, and would be expected to be effective for its intended use, and this of course at the pre-clinical level. It does not produce adverse tissue reactions. It is not systemically toxic. It wasn't antigenic or immunoreactive. It did effectively inhibit peridural scarring in the rat and rabbit laminectomy models.

As I said, this is pre-clinical data. This particular prediction of safety and efficacy, has, at the present, been confirmed by the results which will be discussed from clinical trials with ADCON-L.

With that, I would like to introduce Dr. Jeffrey Ross, who will talk about the MRI imaging.

DR. ROSS: Thank you very much. Good morning.

I'm Jeff Ross. I'm a consultant for Gliatech, however, I do not own stock in the company. I was the neuroradiologist for both the pivotal European trial, and the U.S. trial. I have authored multiple publications on MR imaging of the spine, and particularly the post-operative spine, and co-edited the book, "MR Imagining of the Spine."

The purpose of this talk, brief as it is, is two-fold: to give an overview of the proven utility of MR in the evaluation of epidural scar; and secondly, to more specifically define the MR protocol used in the pivotal study.

As you can see on the slide on the left, the literature has repeatedly shown the validity and reproducibility of MR in assessing not only disc herniations and the presence of scar with disc herniations, but the presence of scar by itself. This has been shown in these studies relative to surgical findings. Epidural scar is clearly identified by three months post-operatively.

If we look more closely at some of these studies, we can see the very high sensitivity of MR imaging, looking at the presence of disc scar and disc and scar. Then on the right-hand side, just to look more briefly at the Fandino article, just to make the point that not only can MR define

a presence of a disc herniation and the presence of scar associated with a recurrent herniation, but also defines epidural scar by itself.

Next I would like to look at the protocol that was used more specifically. This was purposefully designed to be easily followed and reproducible. It used two dimensional T1- and T2-weighted spin echo imaging priority to contrast administration. Contrast was then given intravenously, and then axial and sagittal T1-weighted spin echo images were obtained post contrast administration.

Now importantly, the slices used, particularly the axial index images, which were used for the grading of the scar, were four millimeters in thickness. They were performed in what is called a gap and fill fashion, so that there were no gaps in between the imaging slices which might be missed or not interpreted. That is commonly used, that type of gap, in routine MR imaging.

With MR, scar is clearly identified within the epidural space, and due to the high contrast to noise that we have with MR, because we are looking at epidural fat, which is quite high signal intensity, scar is relatively low signal intensity compared to that, and on the other side we have very low signal intensity on a T1-weighted image of the

CSF that is present within the thecal sac.

Scar tissue consistently enhances following contrast administration. So it is that combination of the morphology on the unenhanced study, as well as the homogeneous enhancement that we see post-contrast that makes the identification possible.

As an example of this, on the left-hand slide is an example of an unenhanced T1-weighted axial spin echo image. We can see the patient has had a right-sided hemi-laminectomy. The usual high signal intensity epidural fat is lost. Here is the normal high signal on the patient's left. On the right-hand side this is all replaced by the epidural scar that is circumventually going around the thecal sac, and we have lost the margin with the dura.

On the right-hand side is the post-contrast axial T1-weighted image. Here we see enhancement of the epidural scar nicely outlining the margin of the thecal sac, as well as defining the margin of the posterior aspect of the annulus.

Now here are a couple of examples of patients not in the trials, but just to give you a flavor of MR looks like for these different pathologies. This is an example of enhanced axial T1-weighted image showing a disc herniation.

Here we see it of low signal intensity, surrounded by some high signal intensity granulation tissue. Then we see low signal intensity CSF, and then facets more laterally, quite different from the enhancing appearance of epidural scar.

On the right-hand side is an unenhanced axial T1-weighted image just showing a patient who has a fat graph placed, showing the signal intensity of the fat, of course showing as fat elsewhere in the body, and again, starkly outlined against the lower signal intensity of the epidural scar. Again, contrasted against the very low signal of the CSF.

Now let's look at little bit more at the scoring system that was used for the trials. If five slices were looked at and scored centered about the disc space, the three central slices were used for data analysis. In any one of these slices it was then broken down into four quadrants based about perpendicular lines drawn from the central aspect of the thecal sac.

So those these quadrants, A, B, C, and D -- each of these quadrants was then graded by the area of involvement of scar within that quadrant. The grading scheme is shown on the right, where a lower number is given to less of an area of involvement, and a higher number is

given to a larger area of involvement within that quadrant.

So let's take an example of this scoring system. On the left-hand slide, and as left-hand panel we see the perpendicular lines have been drawn about the central aspect of the thecal sac. Please contrast the normal appearance of the epidural space on the patient's left-hand side, the high signal intensity epidural fat, the exiting nerve root. Then about the right-sided exiting root we see epidural scar tissue which is surrounding it, but a small amount, and that was graded as a one.

On the right-hand side of this slide we see in contrast what a scar of four looks like, where here in this quadrant there is virtual obliteration of the usual epidural fat in this patient.

So to conclude, MR is really the gold standard for looking at soft tissues in the lumbar spine. We can easily identify the epidural space, the thecal sac, and identify epidural scar tissue. We can see scar three months out following surgery, and using this combination of the enhanced and unenhanced images, we can be sure that we are dealing with scar tissue, and not some other pathology. So we believe this is a valid scoring system used to determine the effectiveness of ADCON-L.

With that, I will end and turn the podium over to Dr. Russell Hardy, who will discuss the pivotal multi-center trial.

DR. HARDY: Thank you, and good morning. My name is Russell Hardy. I serve as a consultant to the Gliatech Corporation. I do own some stock, which I purchased independently.

I am also Professor of Neurosurgery at Case Western Reserve University Medical School in Cleveland. I'm the editor of a book on lumbar disc surgery. I have published a number of articles on spine surgery. I have served as chairman of the Joint Section of Spinal Disorders of the American Association of Neurological Surgeons, and I'm currently chairman of the Spine Committee of the World Federation of Neurosurgical Societies.

I'm going to talk about the pivotal multi-center study which is the basis of our submission to the FDA. Now this study had several objectives: the first was to monitor the safety of ADCON-L; the second, to test the primary clinical hypothesis, namely, that the use of ADCON-L would reduce peridural scar as measured by MRI.

There was a test of secondary clinical hypothesis, namely, that the use of ADCON-L would improve patient

outcome. There were certain other evaluations, including association between scar and clinical outcome, and some observations on a number of patients who underwent reoperation.

The methodology was devised by a number of prominent orthopaedic and neurosurgical spinal surgeons, both here and in Europe. The protocol was a prospective, randomized, controlled, double-blind multi-center study. I think this is important to emphasize. The study was blinded in three ways. The patient was blinded. The radiologist who evaluated the MRIs was blinded, and observers at each center were also blinded. So this is a very effective controlled study.

Evaluation were performed at six months post-operatively, and confined to all guidelines for good clinical practice.

I would first like to discuss the parameters of safety assessments. These were performed at one, three, and six months, and consisted of neurological testing, monitoring signs and symptoms of adverse events, and also monitoring wound healing characteristics in ADCON-L treated patients and the control group.

Scar assessments testing the primary clinical

hypothesis were done by a standardized protocol at six months, and were done by a single blinded neuroradiologist observer. In addition, a small number of patients underwent reoperation. This is common with disc surgery. Observations were made on the amount of scar tissue in both ADCON-L and the control group of patients by the operating surgeon. This surgeon graded visual and tactical scores for the scar tissue.

In addition, there were certain clinical assessments performed on patients pre-operatively, and at one, three, and six months including: straight leg raising examination, which is an important indication of nerve root tethering; pain measurements, low back and radicular pain; and most particular outcomes assessments that were derived from a Johns Hopkins activity-related pain questionnaire.

Clinical monitoring was done by BRI Europa in Brussels; data management by the Johns Hopkins School of Medicine; and statistics by STATPROBE of Ann Arbor, Michigan.

There were nine sites in three European countries. All of the investigators were distinguished European spinal surgeons.

Inclusion criteria included: first time lumbar

surgery; herniated disc at either L4 or L5; single-level, unilateral, herniated disc; an MRI consistent with a diagnosis of herniated disc; and the patients had all failed a non-operative treatment, or required immediate surgery.

Patients were excluded who had prior lumbar surgery or chemonucleolysis; who had other significant spinal pathology; who had peridural steroids within four weeks of surgery; or had an inadvertent incision of the dura during surgery.

You can see the patients in the control and ADCON group. The levels between the control and ADCON group were slightly different, but subsequent analysis revealed this had no influence on the outcome. The groups were similar with respect to age, similar with respect to the distribution of radicular pain, low back pain, had similar straight leg raising pre-operably, and similar activity-related pains.

Then as I noted, the demographics of the disc level were slightly different, but subsequent analysis revealed that this did not affect outcome. The type of disc pathology, however, was similar in the two groups. The patients received similar medications pre-operably. Therefore we can say that the conclusions of this, because

of the similar demographic profiles, that the conclusions of the study will constitute valid scientific evidence.

I would first like to talk about the safety tests. Again, we performed neurological tests, monitored for adverse events, and studied wound healing characteristics. These two slides show ADCON versus control on the operated and non-operated slide. These were similar, except for minor differences at one month, which corrected themselves.

The same is true for motor testing on operative and non-operative sides in both ADCON and control groups; again, transient differences, which corrected and were not significant.

When we looked at adverse events, there was a similar pattern in the two groups.

Finally, we studied wound healing characteristics, and the two groups, the ADCON and the control groups were similar with respect to wound healing characteristics. Therefore, we can say that there was a good safety profile. There were no clinically significant differences from the non-treated and treated groups as measured by neurological tests, occurrence, and clinical signs and symptoms of adverse events or wound healing characteristics. No adverse events were directly attributable to ADCON-L.

I would now like to talk about effectiveness criteria, namely the primary clinical hypothesis, namely, reduction of peridural scar as demonstrated by MRI and also assessed at reoperation. We did study medications that patients received post-operatively to see if this might have an effect. There were no differences between treated control groups. The two groups also received similar maps of physical therapy post-operatively.

The table on the left will show the outcome as measured on MRI. The important thing is that patients who received ADCON were much more likely to fall into a category of patients who had minimal scar on post-operative MRI, and patients in the control group were much more likely to have extensive peridural scar.

On the right is a graph which combines these groups. Patients with non-extensive scar were more likely to have received ADCON, and patients in the control group were more likely to have extensive scar.

As indicated, there were a small number of patients who underwent reoperation. A percentage of patients is known to undergo reoperation following lumbar disc surgery. In the literature this rate is 5-20 percent. The indications are for reherniation, missed fragments,

inadvertent dural tears, or other technical factors.

The reoperation rate in this study was 5 percent control, 8 percent ADCON, well within the guidelines in the literature. Thus, there were 11 patients available for study in the ADCON group, and 6 in the control group.

The surgeons who operated on these patients were asked to grade amount of scar and the tenacity of the scar, particularly the amount of scar anterior to the nerve root, which is the most clinically significant. A three point grading scale of none, moderate, and minimal was used. In the last category were firm adhesions with sharp dissection. This is a surgically important point.

The important thing here is that the ADCON group again, as observed at surgery, were more likely to have no or minimal adhesions. The control group was more likely, and particularly in and about the nerve root, was more likely to have demps(?), sharp adhesions, as observed by the surgeon at surgery. In this method, the surgical dissection was more difficult. It placed the patient at greater risk, and there was a greater chance of complication. So the control group had firm adhesions that required sharp dissection by the surgeon.

So in summary we can say that ADCON reduces

peridural scar. There is a significant decrease in extensive scar. There is reduced scar observed at reoperation, and that the primary clinical hypothesis has been proven.

I would like to discuss the secondary hypothesis, namely, that is improved patient outcome. We measured straight leg raising test. We evaluated low back pain, and most particularly we evaluated activity-related pain, which is, after all, the most important thing to the patient.

On the right you can see a graph that shows improvement in straight leg raising following surgery. The ADCON group at one, three, and six months is clearly superior to the control group. Now the activity-related pain scale was based on the NIH-funded U.S. National Low Back Pain Study from Johns Hopkins. This scale is 0-3.2 scale. Five activities were identified as being particular related to sciatica radicular pain.

There is a clear improvement in activity-related pain in patients who underwent ADCON-L, and in all five the categories, there was a clear improvement in activity related pain. The composite score was significant. Again, this is the thing that is most important to the patient.

So in conclusion, we can say that ADCON has a good

safety profile; that the primary clinical hypothesis has been proven, namely, that there is reduce peridural scar with the use of ADCON; that a secondary clinical hypothesis has also been proven, namely, that there is improved outcome with the use of this device; and certain other evaluations were noted, that there is less scar, and less tenacious scar in reoperation; and that also there is a significant association between scar and clinical outcome.

We can therefore say that ADCON provides a benefit to the patient. It also provides a benefit to the surgeon, and therefore, indirectly to the patient.

Thank you very much. I would like to introduce Dr. Derrick McKinley, who will also provider some supplemental data.

DR. MC KINLEY: Thank you, Dr. Hardy.

The pivotal study is a well controlled, prospective, randomized, double-blinded, multi-center study as previously described. In the pivotal study we demonstrated that ADCON-L was safe and effective in the reduction of peridural fibrosis; that ADCON patients had better clinical outcome; and that the clinical hypothesis of the study had been proven.

We would now like to turn our attention to

supplemental clinical information which supports the results of the pivotal study. We will first present the results of the U.S. clinical trial, which is very similar in design to the pivotal trial, with the addition of the Roland-Morris Disability Questionnaire as a secondary endpoint. This study demonstrates the fact that the pivotal study results are reproducible in a separate controlled study.

We will then discuss the results of the post-study surveillance, which is an analysis of data collected from pivotal trial patients who return for their 12 month visits. The purpose of the study was to collect longer term safety data, and also to prove or support the conclusions of the pivotal study.

Lastly, we will see a surgical video which demonstrates the effectiveness of ADCON-L in cases of reoperation.

I would now like to turn your attention to the results of the U.S. clinical trial, which will be presented by Dr. Donald Johnson.

DR. JOHNSON: Good morning. My name is Donald Johnson. I'm an orthopaedic spine surgeon. I'm an Associate Clinical Professor at the Medical University of South Carolina in Charleston, South Carolina, where I also

sit on the board of trustees. I'm the Medical Director of the Carolina Spine Institute. I have no financial interests or stock in Gliatech Corporation.

I am here to present the interim results of the U.S. multi-center clinical study, which you will see backs up and reinforces the results that we have seen in the pivotal study presented by Dr. Hardy.

Our objectives of this study were firstly, to demonstrate the safety and effectiveness of ADCON-L compared to the no treatment control. We monitor safety. As in the pivotal study, our primary clinical hypothesis was reduction of peridural scar. Our secondary clinical hypothesis, which is improved patient outcomes, was measured with the Roland-Morris Disability Questionnaire.

Our methodology included a consultant panel, and our protocol, again, very strong, as the European study, was prospective, randomized, controlled, double-blinded, and multi-centered. I'll make a point of the double-blinding being the patient and the evaluators. The surgeons were not blinded obviously. They were not the evaluators of this study, except in the redo surgeries that we'll see. Also blinded was the neuroradiologist.

The evaluations made with MRI were done at six

months post-operatively. We used good clinical practices, using IDE regulations, IRB review, and patient informed consents.

We had 16 primary clinical study sites in the United States. These sites are well distributed across the United States. They included a number of orthopaedic and neurosurgical spine surgeons.

Our interim data analysis was preplanned in our protocol. This was performed when about half the patients had completed the six month follow-up visit. The number of patients available is 165, who had completed a six month follow-up, had met all the previously described inclusion/exclusion criteria, and were enrolled between January 19 and August 31, 1996. We thus had 77 control and 88 ADCON-L patients to evaluate.

Our demographics, as in the European study, were very similar between the control and the ADCON-L groups in regards to gender, age, radicular pain, Roland-Morris disability scores. Our operative levels at L4/L5 and L5/S1; again, this is a single level, unilateral problem that we're dealing with here. Our disc pathology is rated by surgeons is also very similar in both groups.

Adverse events related to the procedure or the

original condition were very similar in both the control and ADCON-L group; and also medical events not related to the procedure or original condition are very similar between the two groups.

Thus, we conclude that we have a good safety profile. There is no clinically significant difference from the no treatment group in comparison with the ADCON group in regards to occurrence of adverse events or medical events, and certainly no adverse events attributed to ADCON-L.

Next, we would like to look in regards to the primary clinical hypothesis at the reduction of peridural scar. This was demonstrated by MRI and also in a few reoperations that we have in the U.S. interim study.

The methodology has previously been described to you by Dr. Ross. I'll turn your attention to the graph on the right here. The ADCON-L is in yellow. You can see that the extensive scarring was more commonly seen in the control group, whereas non-extensive scarring is much more commonly seen in the ADCON-L group.

In regards to the few reoperations that we had in this study, the results again were very similar to those seen in the pivotal study. The majority of ADCON-L patients had no or minimal adhesions, and control patients had the

typical firm adhesions requiring sharp surgical dissection.

Thus, we feel the ADCON-L shows a significant decrease in extensive scar; reduced scar also observed at reoperation, and our primary clinical hypothesis has been reconfirmed in the U.S. interim study, as was seen in the pivotal study.

We looked at improved patient clinical outcomes with a slightly different methodology using the Roland-Morris Disability Questionnaire. This is a questionnaire that involves 24 statements concerned with sciatic pain and how it interferes with daily activities, work, and recreation. Total scores at six months can be seen here, with a significant reduction with the ADCON-L group. In this questionnaire, for almost all activities the ADCON-L treated patients had better results. In these five particular activities, these were significantly different results.

These two slides show all 24 activities that are outlined in the Roland-Morris Disability Questionnaire. In 22 of the 24, the ADCON-L group is less; in two they are equal; in the five that are highlighted, as in the previous slide, they are significant decreased in the ADCON-L group.

Thus, in conclusion, we feel the interim results

of the U.S. study support what we have seen in our pivotal study. We have demonstrated in the United States study, a good safety profile. Our primary clinical hypothesis has again been proven, with reduced peridural scar seen by MRI, and also in the few reoperations. Our secondary clinical hypothesis of improved patient outcome has been proven with the Roland-Morris Disability Questionnaire.

Thank you. I would like to re-introduce Dr. Derrick McKinley.

DR. MC KINLEY: Thank you, Dr. Johnson.

Supplement information to our pivotal trial will be presented now. The pivotal study was designed to evaluate the safety and effectiveness of ADCON-L at six months. We have demonstrated the fact that the six month time point is more than adequate to assess the safety and effectiveness of the device, however, we collected additional information from pivotal patients who returned for 12 month evaluations. We would like to share those results with you in this post-study surveillance presentation.

The objective of the post-study surveillance was to evaluate the longer term safety of ADCON-L. I would first like to discuss the results of the safety assessments.

As you can see when we look at the slide on the left, the results of the neurologic exam, there were no differences between the ADCON and control group in any of these neurologic events.

We also assessed wound healing, as was assessed in the pivotal trial, and we looked at the typical parameters that are important in wound healing, and we found there to be no significant difference at this longer time point between the ADCON and control group.

We then assessed adverse event data from patients after the conclusions of the pivotal study, and found there to be little additional adverse event data reported at the post-study surveillance point. This serves to confirm the fact that the six month time point is adequate to assess the safety of the device since the vast majority of adverse event information was collected during the first six months in the pivotal trial.

When we look in more detail at this adverse event data, we see that there is no difference in the distribution of adverse event data between the ADCON and control groups. So in summary, we can say in this post-study surveillance that we have an excellent longer term safety profile of ADCON-L. There were no adverse events directly related to

the use of ADCON-L.

We would now like to turn our attention to the results of scar score analysis, which was the primary endpoint in the pivotal study. This is the same series of slides that were presented in both the pivotal and the U.S. You look at categories of minimal, moderate, extensive, you can see at the longer term time point there are a higher percentage of ADCON-L patients with minimal adhesion or minimal scar, and then there is a higher percentage of control patients with extensive scar.

Looking at categories of extensive versus non-extensive -- the non-extensive is the combination of the minimal and moderate -- we can again see the same significant trend in the results. That is that the ADCON had less extensive scar, and that the control patients had a less degree of non-extensive scar. The ADCON patients conversely had a higher degree of non-extensive scar.

So in summary, we can say that in the post-study surveillance, we have demonstrated ADCON patients have less scar. The primary clinical hypothesis remains proven, and this serves to support the results of the pivotal study.

We last would like to turn our attention to clinical outcome. In clinical outcome we evaluated

activity-related pain, low pack pain, and straight leg raise exam. When we looked at activity-related pain, we find that the mean difference between the ADCON and control group is maintained, and that this difference approaches statistical significance.

Viewed graphically, we can see very clearly that the benefit between the ADCON and control group is clearly maintained through the 12 month time line.

We would now like to turn our attention to a summary of the straight leg raise exam at 12 months. As we can clearly see, there is a significant difference between the ADCON and control group vis-a-vis the straight leg raise exam results through the 12 month time point.

What is important about this observation is that it correlates to what Dr. Spencer described about the neurodynamics in which scar entraps and binds the nerve root, affecting leg pain during the straight leg raise exam.

In conclusion, we have clearly demonstrated the fact that ADCON-L has an excellent safety profile at this longer term time point. We have confirmed the reduction of peridural scar. We have demonstrated the continued patient improvement, and this study also serves to confirm the point that at the six month time point, and the results in the

post-study surveillance are predictive of longer term patient outcome.

I would now like to turn the podium over to Dr. Francois Porchet, who will show you a couple of reoperation videos with and without the use of ADCON for illustrative purposes.

DR. PORCHET: Good morning. My name is Francois Porchet. I am an Associate of Neurosurgery Department at the University Hospital in Luzern, Switzerland. I am responsible for spine surgery, and for its research. I was a principal investigator of the pivotal study, but I don't have any financial interest in the company.

What you are about to see in the following videotape are three surgical cases which demonstrate the effectiveness of ADCON-L. The first case is a non-ADCON patient. It is a bilateral operation, which will demonstrate on side an average recurrent disc herniation operation, and on the other side, a first time disc surgery.

The second case is a post-laminectomy case, also without ADCON-L, which will show an even more severe fibrosis.

The final case is an ADCON patient who had reoperation, and he received ADCON at first surgery. It

will demonstrate the effectiveness.

So the first case is a 40 year old male who had five months after the first surgery, recurrent disc herniation. Here you can see the recurrent site. We are focused on this. There is a tenacious scar tissue covering the interlaminent zone. The surgeon has to dissect sharply the scar tissue with the scissors. This can potentially be harmful for the neural structures, because he can't see them. They are hidden through the scar tissue.

He tries to find the cleavage plane between the scar tissue here, and the nerve structures. He is going a little bit above. This is time consuming. Usually reoperation increases the time by one and a half because of this difficult dissection. It can also provoke excessive bleeding, and you have excessive nerve root manipulation to try to find the cleavage plane between the nerve structures, and finally, the pathology.

Again, he has to sharply with the scissors, dissect to finally find the thecal sac with the nerve root, and underneath, the recurrent disc herniations. He takes it out with his forceps.

Now we are on the other side of the same patient. This is straightforward surgery. After taking away the

ligament, he is just done. There is no sharp dissection. He finds the disc over there, and no manipulation excessive of the nerve root.

This is an overview of both sides; nerve roots are free.

The second case is a 46 year old female without ADCON again. She had a previous laminectomy. You see here even a more tenacious scar tissue. The surgeon has to take a lexal(?) to take away part of the scar tissue. The nerve structures are underneath here.

He tries to find the cleavage plane. Here is the midline and neuro structures. Finally, he decides to go more far lateral, to find the cleavage plane. He has to undercut the article of facet to try to find the normal structures. So this is potentially also no more minimal invasive, because he takes away part of the articulation, and can be the cause of instability.

This is the last case. You see here an MRI, the recurrent disc herniation. The patient had at prior surgery, ADCON-L. So in contrast of what you saw before, there is no sharp dissection. There is no or less tenacious scar tissue. The surgeon can go down only with the nerve hook to do a blunt dissection, and with less manipulation of

the nerve root. He, straightforward, can find the recurrent disc herniation.

It looks almost like a first time lumbar disc surgery, and therefore it takes about the same time as a first time lumbar disc surgery, without bone removal, without sharp dissection, with the potential danger to the nerve structures.

So in conclusion, based on the evidence of these videotapes, and the experience of myself and my colleagues, ADCON-L is clearly effective. In addition to the benefits demonstrated in these reoperations, cases ADCON-L is safe and provides patients with improved clinical outcome, less pain, and a higher quality of life after discectomy.

Thank you. I will turn now to Dr. McKinley.

DR. MC KINLEY: Thank you.

I would like to conclude the presentation material that you have seen over the last 50-so odd minutes. We have discussed the fact that peridural scar contributes to a significant medical problem. In addressing this problem, many surgical and adjunctive medical treatments have been developed and tried, but none have been proven to be successful. As a result, ADCON-L was developed.

ADCON-L is a gel, not a spinal implant, designed

specifically to cover and protect neurological structures from post-operative adhesions. In our pre-clinical work we demonstrated ADCON-L is safe and effective in animal models. In order to evaluate ADCON-L, it was necessary to develop and valid an MRI system in which scar could be assessed.

MRI with gadoliumium is the gold standard for the identification of peridural fibrosis. It is accurate three months post-operatively. The MRI protocol and scar scoring system developed by Dr. Ross is reproducible, and results in a validated technique for the assessment of peridural fibrosis as described in peer reviewed literature. This validated system, which is being used in other clinical studies, is sensitive enough to determine the effectiveness of ADCON-L for the reduction of peridural fibrosis, as previously described.

Having established the safety and effectiveness of ADCON-L in our pre-clinical trials, and having identified and validated a measurement system, we then began our pivotal clinical trial. The clinical pivotal trial was designed to assess the safety and effectiveness of ADCON-L. A summary of the safety results are shown on the slide on your right. What you can see from all of the studies is the fact that the incidence rate of adverse events is very

similar between both the ADCON-L and control group. So what we can say is that ADCON has an excellent safety profile.

I would like to review the results of our primary clinical endpoint for the studies, and that was the reduction of scar. As you can see, it is summarized on the slide on the left. In our pivotal study we showed a decrease in extensive scar. All of these were highly significant. This was confirmed in the post-study surveillance, which was at 12 months, and this was also reproducible in a separate clinical trial here in the United States.

I would now like to turn to the results of the clinical measurements. On your right is the slide previously shown from the straight leg raise exam at both 6 and 12 months. As you can clearly see, there is an ADCON benefit that is maintained through the 12 month time point. This is important, because it correlates with our primary endpoint, the reduction of peridural fibrosis.

I would now like to summarize the results of the activity-related pain analyses. On your left you can clearly see that ADCON-L patients experience less activity pain through 12 months. As shown on the right, this was statistically significant in our pivotal trial at six

months, and approached statistical significance at the 12 month time point.

In the U.S. study we introduced the Roland-Morris Disability Questionnaire. This questionnaire is a well established instrument for assessing patient outcome, as previously described. As we presented, the ADCON group has statistically better results than the control group, and for 22 of the 24, they had better results.

This is a summary of the results from those individual activities which were significant. These results were impressive, considering that these are interim results from the U.S. trial, and represent less than half of the patient population.

From the pivotal study were also able to ascertain a number of associations between scar and clinical outcome. What we found independently was that there is an association between scar and activity-related pain, straight leg raise, and low back pain.

So in conclusion, through the pivotal trial, which is the basis of this PMA submission, we have clearly met the primary and secondary endpoint. The results of this study have been recently accepted for publication by a peer reviewed orthopaedic surgery journal.

From the interim analysis of the U.S. study, we also reached our endpoints. What we demonstrated was the fact that the pivotal trial results are reproducible in a separate clinical trial. In analyzing the results of the post-study surveillance we show that both scar reduction and clinical benefit are maintained over time.

Overall, approximately 460 patients have been evaluated in the pivotal and U.S. trials, and we have demonstrated that ADCON-L is safe, reduces peridural scar, and significantly improves patient outcome. In addition, this product has been administered safely to over 10,000 patients worldwide.

The product under review is shown here on your left, ADCON-L. ADCON-L anti-adhesion barrier gel is to be used during lumbar surgical procedures, providing a physical barrier to inhibit post-surgical peridural fibrosis and adhesions, and the resulting clinical sequelae.

We have provided scientific evidence today which clearly demonstrates that the product is safe, reduces peridural scar, and improves patient outcome. Based on this evidence, we feel strongly that this product should be made available to the U.S. medical community, and of course to the patients who would ultimately benefit from its

availability.

We are requesting that the Orthopaedic and Rehabilitation Devices Panel recommend this product for approval.

Thank you for your attention.

DR. BOYAN: Thank you very much. I think we will proceed immediately to the reviews by the FDA, followed by the major reviews from panel, and then we'll have a discussion period.

**Agenda Item: FDA Presentations**

DR. LEE: Good morning. My name is Kevin Lee. I am medical officer and lead reviewer of this PMA. This is ADCON-L anti-adhesion barrier gel, PMA 960057.

I will introduce the review team. Dr. Glass is a neurologist. Dr. Bushar is a statistician. Dr. Hudson is a molecular biologist. I am a pathologist.

For the FDA presentation, I will provide the device description, animal studies, and the biocompatibility, and panel questions. Dr. Glass will present clinical studies. Dr. Bushar will present statistical analyses.

Device description. ADCON-L is sterile, resorbable medical device composed of porcine derived

absorbable gelatin, USP and a polyglycan ester in phosphate-buffered saline. ADCON-L, a flowable gel, is provided sterile in a kit containing a separately packaged 5 gram collapsible tube of ADCON-L and a separately packaged sterile applicator.

The company has done various non-clinical studies according to GLP regulations. For the toxicity testing of ADCON-L: AMES mutagencitiy test, in vitro hemolysis study, in vitro cytotoxicity study, and modified USP systemic toxicity study in mice, and their results were unremarkable.

For studies of subcutaneous and muscle implantation a acute subcutaneous toxicity study with ADCON-L in rat was done. The finding was that the product was not systemically toxic to the rat. There was more splenic extramedullary hematopoiesis due to inflammatory responses at the implant site, consistent with resorbable properties of the product.

Modified intracutaneous toxicity study in the rabbit was done and showed that there signs of moderate tissue reactions at seven days. The results were consistent with resorbable properties of the product.

Muscle implantation study in the rabbit was done, and showed that the product was classified as a severe

irritant at 14 day, however, the result was consulted to independent experts, and were concluded that the result is consistent with resorbable properties of the product.

For the sensitization study -- with the dermal sensitization study there were signs of delayed dermal sensitization. The results were consistent with the resorbable properties of the product. Hypersensitivity study in a guinea pig injection model was done and showed that the product was classified as a non-sensitizer, or at worst, a mild or potential sensitizer.

For the study of wound healing and peridural fibrosis, wound healing and peridural fibrosis after implantation of ADCON-L and GT 402 were evaluated in a rabbit laminectomy model with histology, and the results were that ADCON-L and GT 402 implant sites exhibited normal wound healing responses with no adverse tissue or biologic responses.

Wound healing and peridural fibrosis after implantation of ADCON-L, GT 402 and GT 003 were evaluated in rat laminectomy. The result was that ADCON-L, GT 402 and GT 003 implant sites exhibited normal wound healing responses, with no adverse tissue or biological responses.

For pivotal ADCON-L effectiveness studies,

laminectomy models. In the previous study, effectiveness was evaluated with a cross-section in the rabbit laminectomy model. The treated group was treated with ADCON-L and the control group was treated with GT 402 solution or laminectomy only. The results are evaluated at 2, 6, 13, and 26 weeks. The findings were that ADCON-L inhibited peridural scar to a greater extent than GT 402 solution or laminectomy only.

In the rat laminectomy model, treated groups were treated with ADCON-L and the control group was treated with GT 003 or GT 402 or laminectomy only. The results were evaluated at 2, 6, 13, and 26 weeks. These findings were that ADCON-L inhibited peridural scar to a greater extent than GT 402 solution, GT 003 or laminectomy only.

Dr. Hudson reviewed the manufacturing process. It is unremarkable. The product used for all the pre-clinical and clinical studies contained a low level of endotoxin.

I will introduce Dr. Glass for a clinical presentation.

Dr. Glass.

DR. GLASS: Post-surgical adhesions --

DR. BOYAN: One moment please, I just need a clarification. That contained no level of endotoxin or low

level?

DR. LEE: Low level.

DR. BOYAN: So it is a microbial produced polyglycan sulfate?

DR. LEE: Yes.

DR. GLASS: Post-surgical adhesions have been implicated in patients' complaints of radicular pain months to even years after initial lumbar surgery, however, the relationship of the two is not entirely clear. It has never been convincingly demonstrated in the scientific literature that peridural adhesions are responsible for or are even correlated with post-surgical recurrent radicular pain.

In other words, there always are seen in clinics across the country, patients who have a lot of adhesions, and very little symptoms, and patients with a lot of complaint of pain and no adhesions or very little adhesions. So the relationship is not clear.

In this clinical review, I will focus on the major features of the sponsor's European study, which provides the central set of data for this PMA. I will also review the U.S. study, which provides supporting data.

On this slide, as has already been mentioned, the hypotheses were that the ADCON-L group would have reduced

peri-operative, peridural fibrosis at six months more than a non-treatment control, and secondly, that the ADCON-L group would have less activity-induced pain at six months as compared to the control.

The subjects entered into the study are given below. These are the intent-to-treat numbers. When it came to six months as far as scar assessment, the number dropped from 147 to 124, which shows a follow-up rate of about 84 percent. The control group goes from 151 to 137, in other words, more like a 91 percent follow-up rate. In the statistical review that will follow, there will be some discussion of the loss to follow-up, and how that might impact the results.

As was mentioned, scar was assessed. Pain was also assessed. In addition to the wARP scores that were mentioned, there were also visual analog scales of pain. That is what referred there under pain assessment. So everybody had to fill out visual analog scales, and I'll explain them a little bit more later, but only those who had pain on those scales were then given the additional assessment tool of the wARP. So you see the numbers are reduced even further, because not everybody was asked to fill out that activity-related pain questionnaire.

The main entry criteria have been presented. Note that radicular pain was an entry requirement, and the patients could have or have not significant low back pain also. As it turned, most subjects, however, had both types of pain.

The methodology has been pretty much elucidated already. The ADCON-L group had gel applied to those areas listed in the middle of the slide. The endpoints were at pre-operative, one month, three and six months post-operatively; so that was the pivotal study.

FDA asked the sponsor to also present the data they had on these same patients carried out through 12 months, and that was reported in their post-study surveillance report. There you see the numbers, so quite a few patients in each group were available for 12 month assessment.

The means of evaluating the scar was the MRI system, as has already been described. Note that the primary endpoint is each subject's maximum score in any of the 12 quadrants. In other words, there were three middle slices on MRI that were evaluated, and each slice was divided into four quadrants, so you have a total of 12 quadrants. It was the highest score received in any of the

12 quadrants that became the patient's scar score.

The sponsor was asked, and did provide data that demonstrated that the results were not affected by whether you considered the score in just one quadrant, or whether you -- let me back up. It was not affected by whether a patient's score was based on extensive scar in one quadrant, or was based on extensive scar in one or more quadrants. So through the scar results that are presented, it is based on the maximum scar score in one quadrant.

A panel question will come up a little bit later as to the adequacy of the MRI evaluation method and the scoring system.

The primary endpoint was the extent of peridural fibrosis on MRI at six months. That was blinded and done by a single independent neuroradiologist. The secondary endpoint was the wARP score. That is the weighted activity-related pain score. The weighting was applied in a manner as developed by Johns Hopkins University.

Effectiveness was defined as the ADCON-L group having significantly less fibrosis on MRI and less activity-related pain.

I'm going to back up and talk a little bit more about those visual analog scales that I alluded to earlier.

These were 10 centimeter scales. The patients filled them out separately for back pain and leg pain, and they were to consider their pain over the proceeding week. When they filled these out for leg pain, they were to consider pain when most severe, pain on average, and pain at the end of an active day. Then they did the same for back pain. So there was a whole set of visual analog scales that were completed.

Then to be complete, a neurological exam was done. The focus was sensory, motor, reflexes, and straight leg raised testing, again, done by a blinded physician.

As far as effectiveness, the focus was the amount of scar. Please keep in mind that these data are all based on evaluable subjects. Please note the bottom row, and that is the extensive scar, so greater than 75 percent scar in a quadrant. You note that a fewer percentage of patients in the ADCON-L group had extensive scar compared to the control group at six months, so it is 38 percent versus 50 percent. That same relationship held up at 12 months; 28 percent and 41 percent.

Also, those differences are statistically significant. The P values are provided below, and those are all based on 2-tailed tests of statistical significance.

Having said that, it should be noted that those

percentages to some, might appear rather high. If you looked at combining the two row, in other words, if you looked at scar 50 percent or more filling up a quadrant, those percentages are higher. In other words, at six months 75 percent of the patients had greater than 50 percent scar, compared to the control group, which was 79 percent. So the results would be very, very similar if you combined the last two scar scores there.

If you look at 12 months, again, if you combined the 51-75 and the 75 percent categories, your total would be 59 percent of patients having that degree of scar, as compared to the controls, where it would be 69 percent. So there are many ways to look at these data.

The important question for the panel of course is going to be, there is reduction in scar scores in the ADCON-L group compared to the control. Obviously, we want to know what clinical ramifications might that have? In other words, what clinical benefit do you see in this kind of a reduction in scar?

We noted that some of the patients were improving in their scar scores from 6 months to 12 months, so we asked the sponsor to provide the data that you see here. The percentages of patients who did make this improvement are

similar across the two groups. It is not at all clear what is accounting for that. The sponsor did provide some speculation as to reasons for that. That may be a point of discussion among the panel a little bit later.

This relates to the activity-related pain score, specifically the wARP. The sponsor did demonstrate that at baseline the mean wARP scores were similar for the ADCON-L and the control groups. The results on the left show what the comparison is at six months. There is a statistically significant difference favoring the ADCON-L group using the 2-tailed test. If you look to the right, that difference is not maintained at 12 months.

I would like to make an additional comment about the visual analog scales. I don't have them up here, but if you look at those results between the two groups at the two time points, none of those comparisons yielded a statistically significant difference.

Also, a word about the neurological testing again. If you compare the two groups, both at 6 months and 12 months, there are no statistical differences.

In terms of the straight leg raising, we focusing on the testing done on the operative side. If you look at that side at 6 months and 12 months, and if you look at data

separated into three categories, in other words, number of patients who got better, number who stayed the same, number who got worse on their straight leg raised testing, and if you look at the statistical difference using a 2-tailed test, none of those differences were statistically significant.

The sponsors already explained the reoperations. The numbers were rather small. There were only 13 reoperations in 12 patients in the ADCON-L group, and 8 patients in 8 patients in the control group. So there is not a lot of data here in which to draw firm conclusions.

This is a rather inclusive list of all the safety events that occurred between the two groups. When I say all inclusive, this is it. These are the minor things, lumped with the more major things. As you go down the list, you will notice that they line up pretty consistently across the two groups.

Also in terms of motor deficit, sensory deficit, it is not real clear how many of these are really things you would call a neurological deficit. Some of these were slight abnormalities on certain features of the neurological exam. You would hardly call some of those variations deficits. Then it is also not clear how many of these were

permanent and how many were transient. So you've got the complete number, and we can't really make too many more distinctions than that.

This has already been presented, and it shows that almost 93-95 percent of the events that did occur, occurred within the six months, and you got very few events after the six month period, and that was the same for both groups.

I'm now going to go to the U.S. study. This is to be regarded as supportive data, and the results are not final results, but interim results. The hypotheses for this study were very similar. In the statistical review to follow, there will be more comment on the drop out. You see from the amount that were entered to how many you had at follow-up. Again, this has not as much significance, since this is an interim study.

The main entry criteria are listed there for you. The follow-up was pre-operative, one, two, and six months. The difference here in the scoring system was the use of the Roland-Morris Activities Performance Questionnaire, which has already been described. This is 24 statements that the patients had to say whether pain was produced by specific activities. When they filled that out, they were to fill it out based on that particular day they completed it.

Terms of effectiveness endpoints, specifically amount of scar at six months in evaluable subjects; you see the percentages there. Fifty-four percent of patients in the ADCON-L had extensive scar, while 77 percent of control patients had extensive scar. If you combined the bottom two rows, it is 84 percent for the ADCON-L group, and 91 percent for the control group.

So while there was a statistically significant difference across groups, and that was based on the 2-tailed test, the percentages are still high. These percentages are even higher than the European data, and that is not entirely clear why these percentages would be higher. The point is that with the device, you are not seeing dramatic reduction in peridural adhesions. It is still quite extensive, but there is a difference between the two groups, so ADCON-L is producing more of a benefit than no treatment at all.

When it came to the wARP scores, no significant difference between the two groups. Not shown here, but if you look at the visual analog scales for pain, again, there were no significant differences across groups.

The Roland-Morris. The means here are statistically significant. This is based on a 2-tailed test. It is not entirely clear that the two groups were the

same at baseline, and Dr. Bushar in his statistical review, is going to touch upon this point.

Then before I leave that, in terms of reoperations, again, there was very little data. There were only six reoperations in the ADCON-L group, and two in the controls, not enough to draw any conclusions.

Adverse events; looking at the table you see very similar percentages across both groups in the U.S. study. If you looked at them specifically -- I don't have that up there -- but again, the nature of these events were very similar both groups.

These next two slides try to make a comparison between the European and the U.S. data. If you look at the European data in the last two rows, and you go down, you see the differences between 6 months and 12 months in terms of patients who have extensive scar, and you notice there is improvement from 6 months to 12 months, and we have alluded to that already; and that held true with the control group. So both groups did show some improvement in the amount of extensive scar from 6 months to 12 months.

Then as already noted, if you look at the European at six months and U.S. at six months, there are differences in the percentages. The percentages are higher in the U.S.

group, but the difference between the two groups is maintained.

This just shows you that the adverse events when you look across both studies, are very, very similar.

Overall, and this is from both the European and U.S. data, based on the MRI method presented, it was demonstrated that the ADCON-L group had significantly less peridural fibrosis post-operative than the untreated control group. This finding was demonstrated at 6 months in both studies, and at 12 months in the European study.

The ADCON-L group had significantly less activity-related pain than the control at six months in the European study, but this finding was not confirmed in the U.S. study. The European finding was not maintained at 12 months.

Then finally, the ADCON-L and control groups did not differ significantly in terms of adverse events.

Dr. Bushar will now present the statistical review.

DR. BUSHAR: Thank you, Dr. Glass.

Good morning. My name is Harry Bushar. I'm a statistician with the Center for Device and Radiological Health. What I'm going to do today is take you through the sponsor's clinical trials for the third time. I want to

emphasize certain things that weren't emphasized earlier. I'm going to look at these trials from the point of view of some of the additional analyses we asked the sponsor to do.

All of what I'm presenting are the sponsor's analyses, not my own. I did check the sponsor's work, but I am not presenting my own work; I am presenting the sponsor's work.

What I asked for was intent-to-treat analysis to try get as many patients as possible into the analysis. This was done by finding substitute data that could be found by using the worst case. The sponsor was able to do this, and I'm going to present these results now. I'm going to focus on effectiveness, and I'm only going to be talking about those effectiveness endpoints that were statistically significant, and I'm always going to be using a 2-tailed P value. I'm going to be using 5 percent as the significance level.

The main thing I want to talk about today is the pivotal European multi-center clinical trial for ADCON-L. The design was prospective, randomized, double-masked, which means that the patient did not know whether they were being treated, and the evaluator did not know. It was multi-center. The control was a no anti-fibrosis treatment

control, which meant that nothing additional was done to the patient after the operation was completed.

As far as randomization goes, there were 298 patients who were randomized equally to ADCON-L and the no anti-fibrosis treatment control. These groups were randomized within each of the nine centers separately, so that a balance was maintained between the two groups at each of the nine centers.

As far as completers go, we have 267 or 90 percent of all the patients randomized actually completed the 6 months.

I'm going to mention safety briefly, because there is no statistical significance here. The adverse events occurred with similar incidence between the ADCON-L patients, 35 percent, and the control patients, 39 percent.

As far as effectiveness goes, the primary outcome criterion was that ADCON-L will reduce the extent of peridural scar relative to control at six months. The method of analysis was the Cochran-Mantel-Haenszel -- or CMH as I refer to it later -- procedure, which was stratified by center. The sponsor always put center in the model, which meant that each center was looked at separately, and then they were combined for the final P value.

Now the intent-to-treat or ITT patients, analysis of all 298 patients randomized indicates statistically significant MRI scar score reduction at six months with 2-tailed P, which is 0.02.

The secondary outcome criterion was that ADCON-L will reduce the extent of activity-related pain or ARP, relative to control. The method of analysis was the same as before, CMH results stratified by center. This is an analysis that we asked the sponsor to do. We tried to get as many patients into the study as possible by adding those without pain back in, but counting them as 0. That's why we had to go to a CMH procedure, rather than the procedure that the sponsor had used to analyze the data where those without pain were excluded.

So now I have all 267 evaluable patients with or without pain, which represents 90 percent of all randomized. This analysis indicates that statistically significant ARP radicular factor score reduction at 6 months with a 2-tailed P equal to 0.04.

There was an additional assessment, and that was for the intent of showing that the extent of peridural scar is predictive of six month recurrent radicular pain or RRP, without regard to treatment. Here the sponsor combined both

the treatment with the ADCON-L and the control groups, because the question had nothing to do with ADCON-L, but simply whether or not that you could use scar score to predict recurrent pain.

The method of analysis here was logistic regression. The result was for the 201 patients that actually met the sponsor's criteria, mainly, they had to have recurrent pain less than or equal to 4 at one month, in other words, the operation had to be a success in terms of pain; then it had to return again greater than 4 at six months. In other words, you had to have recurrent radicular pain.

Now this is only 67 percent of all the randomized patients, but in this analysis the scar score did statistically significantly predict six month RRP or recurrent radicular pain with 2-tailed P equal to 0.02.

I want to point out though that this is 67 percent of all the patients, because of all the criteria that had to be used to get down to a group that they could actually look at. So what happens when you do that, when you reduce or remove one-third of your patients is it is very difficult now to generalize this. What does this actually represent? It represents a subset of the patients, but we don't know

exactly what this means in terms of all the patients, because of the way it had to be done.

There was a supplementary assessment, and that was to show that ADCON-L will reduce the weighted ARP, which is the secondary criterion for effectiveness. Now this is done over time, relative to the control for months three through six. This was a repeated measures, and again, it was controlled for by center.

The result was that for 198 intent-to-treat patients with pain -- they did not do this for the patients that had no pain -- which represented 66 percent of all the patients randomized, the analysis indicates statistically significant weighted activity-related pain score reduction over the time from three months through six, with a 2-tailed P equal to 0.03.

This sort of extends the result of focusing just onto six months, and trying to look over at least the latter half of the experiment, when the weighted activity-related pain should have been reduced. They actually did this from months one through six, and it was not statistically significant using a 2-tailed P.

Another supplementary assessment was to account for effects of factors on ADCON-L. This is looking at

potentially clinically significant factors. What we are doing here is we are looking at the primary criterion for effect, which is scar score. The sponsor used an analysis of covariance or ANCOVA. They put in an enormous number of factors. Only two of them popped out as being statistically significant, and that was operative side, whether you went in on the left or right, and the other was use of anxiolytic drugs at one month.

I mentioned those because they were statistically significant. There were other factors in the model, such as center, that were not significant. When you put all this together, what happens is that for the evaluable patients, which is 90 percent of all randomized, even when you correct for everything you can think of, you still get a statistically significant six months scar score reduction, with 2-tailed P equal to 0.03.

Another supplementary assessment; here the intent is to extend the extent of peridural scar reduction for ADCON-L relative to control from 6 to 12 months. This is the post-study analysis that was done by the sponsor. The method of analysis was CMH, Cochran-Mantel-Haenszel, stratified by center, and using all the patients now, the ITT patients. This still indicates statistically

significant MRI scar score reduction at 12 months, with a 2-tailed P equal to 0.02.

Now we are down to the supportive United States multi-center clinical trial for ADCON-L. This is an interim analysis. It is a prospective, randomized, double-masked, multi-center, no anti-fibrosis treatment controlled, clinical trial, the same as the European study. The only difference here is that they have less patients and they have more centers. There were 223 patients randomized equally to ADCON-L and no anti-fibrosis treatment group, and again, this randomization was done within each of the 16 centers to achieve balance.

Completers at the interim analysis were 71 percent or 158 of all 223 patients randomized. These people actually completed 6 months, and were available for analysis.

As far as safety goes, in the U.S. study the adverse events occurred with similar instance between the ADCON-L patients, 37 percent, and the control patients, 40 percent. As indicated earlier, this was also similar to the European results.

As far as effectiveness goes, the primary outcome is exactly the same as in the European study, that ADCON-L

will reduce the extent of peridural scar relative to control at six months. Again, they used the Cochran-Mantel-Haenszel procedure, stratified by center.

For the 158 patients with scar score, that is 71 percent of all patients randomized, the analysis indicates statistically significant MRI scar score reduction at 6 months, with 2-tailed P equal to 0.02, which confirmed the result found in the European study.

As far as the secondary outcome for effectiveness, what the sponsor did was again, they looked at the activity-related pain, but in their protocol they only required that that be numerically not necessarily statistically significantly better than the control, and that is exactly what they found.

So they used another measure, which was not used in the European study, namely the Roland-Morris activities performance. The method of analysis here was analysis of variance or NOVA. Again, they controlled for center. Now for the 160 patients with Roland-Morris score, 72 percent of all randomized, analysis indicates statistically significant 6 month Roland-Morris score reduction with 2-tailed P equal to 0.03.

I have to mention though that there was one thing

left out of this analysis. Even though it was controlled for by center, it was not controlled for baseline Roland-Morris score. Now at baseline these scores were not statistically significant. The P value was 0.26, but there was a difference in the wrong direction. There was more disability in the control group. I think that the analysis should be redone with a correction for baseline. So we can't really be sure that P value is statistically significant.

Thank you very much. I will now return the podium to Dr. Kevin Lee, who will provide the panel with their questions.

DR. LEE: Chairman and panel members --

DR. BOYAN: Actually, why don't we do this one thing. Before you read the questions to us, why don't we go ahead and have the reviewers from the panel review, then have you read the questions, and then we'll take a short break.

Our lead clinical reviewer is Dr. Wilkinson. Are you ready Dr. Wilkinson?

DR. WILKINSON: Yes, I am. I have put down my comments in writing, which I can share with the panel, so the panel can follow along with these comments, which are

rather extensive.

Manufacturing considerations. In the toxin release levels used in the study material was 2.8 EU per grams, but the manufacturer proposes production limits of less than 70 EU per gram. This level seems to meet FDA specifications for parenteral drugs, but is much too high for specifications for interthecally used drugs.

The labeling should clearly state this, but this should pose little risk to the patient if ADCON-L is not used in cases when the dura has been torn. I did note, however, that two of the United States patients were given ADCON-L despite dural tears, and despite their own exclusion criteria.

Animal studies, the biocompatibility studies. ADCON-L was scored as a tissue contact irritant. Whether that was because of primary properties of the material or as absorption process doesn't change the fact that it causes tissue contact irritation.

It also demonstrated evidence of delayed dermal sensitization, and we heard that that has been questioned as significant or not, but that was the report.

In the rabbit study it is not clear how a residual implant material was identified. Once gross pockets of

colored fluid had resorbed, how much of the material remained diffused into and perhaps bound to surrounding tissues, and therefore still potentially biologically active?

There was no MRI correlation in that rabbit study with histologic evidence of residual ADCON-L or scar. Can MRI distinguish between light and dense scar? Can we be sure that diffused or bound ADCON-L does not give dense scar the MRI appearance of light scar?

In the rat study the scar at the ADCON-L site seems to be increasing at six months, according to the tables we were shown, the graphs, yet no later data is available. "Whitish-red fluid, presumed to be ADCON-L, was found at seven of eight sites at two weeks, and this fluid was not observed at later intervals," quoting from the statement submitted.

Yet in the next paragraph we read, "residual implant material was identified at two weeks at all sites, and at six week in one of 13 ADCON-L sites." So which is correct? Or were there other ways of detecting ADCON-L besides the presence of gross collections of fluid?

Now clinical studies, a general comment, free fat grafting is recognized by the manufacturer, and we heard

that again today from our clinician present presenter, to be the standard treatment for prevention of post-operative peridural fibrosis. If that is the case, and if that was presented to human studies committees, I'm surprised that it was not required as part of the control.

If the manufacturer intended to show that their product is superior to alternative, and especially to standard treatments, why was not free fat grafting used in the controls?

Now in the European study it wasn't clear to me whether patients were found to have epidural scar present at the initial surgery, which certainly can occur in patients not previously operated. If so, were they excluded from this study, or was that finding noted?

In the operative technique in the European study, the volume of ADCON-L injected varied between two and five milliliters. That probably relates to the extent of bony removal. Even though this is an important technique variable, it seems not to have influenced outcome in terms of maximum scar score at six months, but no other correlations were given.

Now you could see from the video today, those of you who are non-surgeons, how the available space around the

nerve root is quite limited. The available space above the nerve root in the dorsal quadrant is much greater. That was I think, readily apparent on the video for the non-surgeons.

Now outcome data; overall only 74 percent of the evaluable patients were analyzed at 6 months for association, 15 having been eliminated for data deficiencies, 55 having been eliminated as surgical failures. I wasn't quite sure I understood what that meant.

Drop outs before six month evaluations were twice as common among device subjects as among controls.

The number and type of complications and neurologic findings seem evenly matched between the device and control patients, and seem reasonable.

ADCON-L is a tissue irritant, at least in the pre-clinical studies, and is perhaps rapidly absorbed, though as I said earlier, I'm not convinced that has been demonstrated. However, no data was collected regarding lumbago or sciatica in the first one or two weeks post-operatively. When asked about this, the manufacturer replied, radicular pain over the first two to three weeks was never observed since the patients did not complain of this during the one month visit, and during the period of time between the primary surgery and the one month visit.

Despite this attestation, Table 38 records that 21 percent of device patients and 23 percent of controls reported pain equal to or greater than 4, which means severe pain, at the one month evaluation. So that the reply seems to have been either an error or a prevarication.

Dr. Hardy also mentioned that there were significant neurologic differences in the neurologic evaluations at one month which were transient events.

Now the paper published in Neurosurgery, with which we were supplied, reports a 3.2 times greater likelihood of recurrent radicular pain if the post-operative MRI disclosed extensive scar. That paper refers to itself on page 860 as the first study to quantify peridural scar, and evaluate its correlation with clinical sequelae. It is claiming to be a unique study, showing this relationship.

Despite that paper, no statistically significant reduction was disclosed in lumbago or sciatica in either the European or the United States study in the device group, even though their scar scores were said to be worse than controls.

The paper in Neurosurgery notes that patients were excluded from the study if their pain did not improve post-operatively, therefore biasing the group study. The pain on

average and pain when most severe measures were both analyzed, but only the pain when most severe measures showed significant correlation with amount of scar, so that even in this paper two of three indicators of post-operative pain did not show statistical significance.

Furthermore, the paper comments that logistic regression analysis of the correlation between severity of scar and the incidence of recurrent radicular pain disclosed no statistically significant correlation. Overall, 77 percent of patients demonstrated moderate or extensive scar, yet only 9 percent of these complained of recurrent radicular pain; 43 percent demonstrated extensive or maximal scar, but 83 percent of them did not complain of radicular pain. Thus, this is not a particularly robust clinical correlation.

The editorial comments at the end of the paper, which were not included in the panel pack binder, generally emphasized that recurrent radicular pain may be more a function of surgical technique than of MRI-detectable scar.

Now it is not clear whether the extent of epidural scar correlated with the density of scar as seen on MRI. If some control patients had free fat grafts, that also could alter MRI appearances. It is also not known whether

diffused or bound ADCON-L alters MRI scan appearance.

The rat study suggested that epidural scar was increasing at six months, which could certainly happen if the protective effect of ADCON-L is operant only while the material is present, and if the material is indeed absorbed completely over time, however, human data seem to indicate a reduction in the extent, not the density, of MRI-detectable scar at 12 months, suggesting that scar resorbed or became less MRI detectable, or that the detection quantification techniques used were unreliable, or unstandardized.

Now the frequency distribution of extent of scar seen in the anterior quadrant around the nerve root on MRI scan is not linear. There are far more patients exhibiting extensive or moderate scar than minimal or no scar. In fact, in the European study moderate or extensive scar was found in 85 percent of device patients, and in 91 percent of control patients, with extensive scar in 28 percent and 41 percent respectively. This non-linearity was even more pronounced in the U.S. study, as I will comment later.

Thus, even if scar reduction in terms of extent of scar, did reach statistical significance, the reduction in scar was not robust. Scar was rarely reduced to below moderate levels.

Furthermore, when patients were reoperated, moderate or firm scar -- not talking about extent of scar, but the density of scar, probably a more important clinical variable -- was found above the dura in the area of dorsal bony defect more often in device patient than controls, 45 percent versus 33 percent, even though this is the area where the bulk of the ADCON-L is left. So where the ADCON-L was left in largest quantities, scar was more dense, not less dense.

Post-operatively radicular and low back pain were characterized either by improvement or on an analog scale, but no statistically significant improvement could be demonstrated for most severe pain, or average pain, or for pain at the end of the day. If a major clinical goal using ADCON-L is to reduce post-operative pain, and especially sciatic pain, this was not achieved.

The weighted activity-related pain, the wARP score, was reported to demonstrate statistical significance, but there are several concerns. Patients were not administered this test if they reported no pain on the other tests, eliminating over 30 percent of the test subjects, and even more later in the U.S. study, therefore altering the N for statistical calculations.

Dr. Bushar told us that with an intent-to-treat analysis, the statistical correlation still reached P equal 0.04, which is not dramatic, but is still statistically significant, however, we have no assurance that patients would not have reported pain on some of these activities, but by avoiding these particular activities, they were able to avoid pain in their daily lives. They have been having no pain, because they didn't do those things. Had they been asked, do those things cause pain? They might have responded, yes.

Furthermore, the five categories chosen as most associated with radicular pain clearly are capable of causing mechanical back pain as well, for instance, bending and lifting. This type of pain often radiates to the posterior thigh, and then it is frequently reported as leg pain.

The weighting given to these activities is clearly arbitrary. Responses to the questionnaire were reported merely as yes or no, and were not quantitated, nor is there a reporting given of where pain was experienced. Thus, the device patient who experience severe pain on all current activities would receive the same score as a control patient who experienced only mild pain on all five activities. A

device patient who experienced severe sciatic pain on only four activities would have actually received a better score.

Finally, the wARP score did not reach statistical significance at the 12 month follow-up. So even if there is some relief, it seems to be transient.

Now Dr. Spencer reminded us today that straight leg raising is a cardinal sign of nerve root fibrosis for the clinician. Straight leg raising or SLR improved at six months in 94 percent of the device patients, and 87 percent of the control patients on the operated side, but they also improved in 39 percent versus 26 percent, or a greater degree of improvement in the unoperated and untreated side.

This observation was maintained at the 12 month level, at 12 month evaluation. SLR was unchanged in 4 percent of device patients, and 10 percent of control, but it's not known how many of these patients had normal SLR pre-operatively. Improvement did not reach statistical significance. Since limitation of SLR is a cardinal clinical sign of nerve root entrapment by epidural scar, this does not confirm a protective effect of ADCON-L.

Now in the United States study, a general comment, this study has not been completed as of the time of this panel meeting. MRI data, moderate or extensive scar was

seen in an incredibly large number of patients in both groups; 95 percent of device patients, 97 percent of control patients, with extensive scar in 54 percent and 77 percent of the control patients respectively.

Does this mean that United States surgeons are technically inferior to their European counterparts? Or were MRI rating techniques indeed subject and variable?

Clinical outcomes. The Roland-Morris activities performance scale was described as a secondary criterion for evaluation of device success, but so also was a quantification of radicular pain, which is generally considered by clinicians to be one of the principal indicators of symptomatic epidural scar.

The available data demonstrates no statistically significant improvement in radicular pain, and overall low level of radicular pain in both groups; on an analog scale of 0-10, mean score of 1.46 for device patients, and 1.84 for controls, even without fat grafts. This also fails to demonstrate an effectiveness for ADCON-L in one of its chief desired results.

The question asked for wARP scores were not administered to 40 percent of the subjects in this study, but the results were almost identical for those that were

studied, with only small positive score; 1.43 versus 1.47. This is strikingly different from the results of the European study at six months, and calls into question the clinical significance of that study's results.

The Roland-Morris activities performance scale, which we heard was not corrected by baseline scores, records the sum in a scale of 0-24 of activities involving radiculopathy-related impairment, but again, it does not quantitate the severity of impairment of pain, a potentially damaging omission.

Nonetheless, there was impairment of activity in only 2.2 of the 24 categories for device patients, and 3.8 of the 24 categories for control patients. With such numbers of activities impaired, even if numerical statistical significance was reached, this seems to have little clinical significance.

Now in the summary statements and package insert drafts that we were supplied, the draft package insert summary of safety and effectiveness, and summary of data and information all present as clinical outcomes, only the wARP results from the European study, and omit discussion of other and less flattering results of clinical outcome assessments from either the European or the U.S. study,

similar to the presentation we heard today. This seems to be deliberately misleading.

The package insert should specify the actual percentage of observation of complications which have a greater than 1 percent likelihood. Since ADCON-L caused delayed dermal sensitization in guinea pigs, there should probably be a cautionary statement about its reuse in humans.

Since permissible levels of endotoxins released are specified by the manufacturer as less than 70 EU per gram, there should be a cautionary statement about intrathecal use, or use when there has been a recognized dural tear.

My final impression is that ADCON-L is probably a safe product, but it has not convincingly been demonstrated to be effective.

DR. WITTEN: Dr. Wilkinson, may I provide a copy of your written remarks to the sponsor, since they will want to have an opportunity to --

DR. WILKINSON: That's your option. Yes, I have no objection.

DR. BOYAN: I would like to now go to our pre-clinical reviewer, Dr. Tom Bauer.

DR. BAUER: I appreciate the opportunity to review this material. It is sort of interesting in a kind of a masochistic way, for us to have these proposals to review, especially the pre-clinical studies. It allows us to evaluate the data in a much greater degree than we are usually able to when we get manuscripts that are submitted for publication, and in so doing, it is natural for us to sort of try and pick out specific things that again, would be missed on other types of scientific studies.

I have been asked to look at the pre-clinical animal studies, and have done so, and would like to comment on those. Now has already been mentioned, there are a number of safety animal studies that were performed. I had not intended to comment on those specifically, but Dr. Wilkinson has brought several to our attention, so I will go over a couple of those.

DR. BOYAN: Dr. Bauer, I would ask just in the interest of time, that if you are going to repeat something that Dr. Wilkinson said, maybe you could shorten it, and then add new stuff as you go through it, that you noticed, that he may have missed.

DR. BAUER: Again, of these various safety tests, two deserve special comment. The first is the acute

subcutaneous toxicity study. In this study, a relatively high concentration of ADCON-L was placed subcutaneously in rats. Changes reflecting local inflammation at the injection site persisted until 16 days in the ADCON-L group, but not in the saline control. This could be interpreted as a local tissue irritant by some observers. All injection sites were unremarkable at 44 days.

The study was initially performed at a commercial lab, and the results were then reviewed by two other consultants. All reviewers eventually agreed that the subcutaneous reaction is typical of that seen for resorbable materials, without any evidence of an immunologic reaction.

Again, I think the phrase "tissue irritant" is a little bit ambiguous, and I think that taken in the context of a material that is expected to resorb, one expects to see a certain foreign body-type inflammatory reaction during a predictable time interval. I personally am not concerned about the subcutaneous toxicity test, or tissue irritant issue.

A second study was performed to determine if ADCON caused a delayed hypersensitivity response. ADCON and several other control materials, including an approved collagen containing product were injected intraperitoneally

to guinea pigs. Two weeks after the final induction injection, animals were challenged by subcutaneous injections and were then monitored for signs of hypersensitivity.

This study was again performed at a commercial lab, and the results were again sent out and reviewed by two other consultants, all of whom eventually interpreted the results to suggest that ADCON-L is either not a sensitizer, or at worst, a very weak sensitizer, and produced in fact less of a reaction than the currently approved procine collagen containing material.

Again, given the widespread clinical use of I guess I need to phrase porcine gelatin derived materials, I am also not particularly concerned with delayed hypersensitivity as a complication of this material.

Now to document safety and efficacy, two additional animal studies were performed, a rabbit laminectomy and a rat laminectomy studies. Both studies were of essentially the identical experimental design. The methods were the same, and the results were basically the same, so I'll kind of lump those together.

Now basically, lumbar laminectomies were performed. In the rabbit study several different levels

were used in each animal. The animals were sacrificed at several time points. The primary outcome variable was the reduction in the amount of density of scar observed at the epidural level. Observations were also made in tissue and bone, but the most relevant observations for us are those around the dura.

Now two types of observations were made to try to quantify the amount of dural fibrosis. The first is the appearance of the tissue based on simply gross dissection, and the second was by histology.

Now within each study, a number of different materials were used, but as an example, within each sacrifice group nine rabbits might have been used to compare the ADCON-L with a sham operation, for example. Now as I understand it, of these, seven were just grossly dissected, and the amount of dural fibrosis was visually estimated. More specifically, the surgical site was opened, and then as an evaluator sort of dissected down to the dura, they graded the scar formation based on visual observations and tactic appraisal.

Now again, it is nice to have all this data to look at, and since we have it, I just had to look at it. I wonder if I could ask somebody from Gliatech to grab one of

their notebooks and look at some of the raw data with me? This is on the rabbit study. I am looking, for example, at volume number 7. My page number 1,751.

DR. BOYAN: Can we reserve this part for the discussion, where that gives them a chance to look at the data? Is it necessary for your review for them to do this?

DR. BAUER: I think if we could just deal with this in a sequential fashion, it would be best.

DR. BOYAN: All right.

DR. BAUER: While we are digging this information out, again, the experimental study described this dissection method with relatively little histology performed. I can see how it would be difficult to design an animal study that would demonstrate fibrosis of this type. I would expect it to be pretty subtle and sort of linear and hard to recognize histologically.

It would be hard to quantify mechanically. It is hard to envision a mechanical test where you would sort of go down and jiggle the dura or something, to get some index of fibrosis.

On page 1,751, this is a consecutive list of animals entered into the study. Animal numbers go consecutively from 47001 to 47118. I was just struck in

going through this that there are about 100 animals that are missing between 47072 and 47181. This happened on June 21, 1993. I wonder if there is an obvious explanation as to what happened to those 100 animals?

DR. ZUPON: This is numbering system that is being used here. Beyond that, we have to go back to tables in labs.

DR. BAUER: Could you please identify who you are?

DR. ZUPON: Mike Zupon, Vice President, Product Development Gliatech.

DR. BAUER: It is just sort of conspicuous, because everything else is so consecutive, and then all the sudden one day we have about 107 animals --

DR. ZUPON: The numbers that are different, these are the Hazelton numbers that basically when the numbers are received. That's the way the animals are basically operated on. This is a very long study. It has 2, 6, 13, 26 weeks. All the surgeries were not done on the same day. There are 128 rats or 80 rabbits.

DR. BAUER: Yes, it's just that all the rest are consecutive numbers.

DR. ZUPON: I would have to go back and check with Hazelton. These are the Hazelton generated numbers, and it

would have to do with the arrival of the animals, and which lot they came in on, and the day the surgeries were actually conducted.

DR. BAUER: You might look, 47039 from June 14, was an animal destined to be grossly dissected at 26 weeks, and in the data for that group, I am unable to find the raw results for that animal. It's probably not of material significance to the outcome of the study.

Based on the gross dissection method of this, the study was done blind. Statistical analyses were done that showed differences in the relative amount of fibrosis. Now I understand when doing studies with multiple samples from the same animal, I have been told that you really need to make statistical adjustments for that such that if I'm doing a study, and I have got six biopsies from one patient, and five from another patient, my N isn't 11.

These animals all had two levels done to do your correlations. Was there an adjustment made for multiple observations from each animal?

DR. ZUPON: Again, each animal had a paired set. So in other words, we randomized the treatment load within a given set of -- it was in the study. So we were comparing the GT 402 component against the ADCON-L component. We

randomized by block into making sure that each animal had one site of each, so each animal kind of acted as its own internal control.

As far as the statistics go, we have a statistical analysis in here. I have to go back to check that, but the statistician did bring up your point, and I believe it was compensated, but I can get back to you on that. Give me two minutes, and I can have someone look at that for you.

DR. BAUER: Again, the gross description is difficult. It was blind study, but it is hard to be too objective about that.

Now, only two animals from each group were done for histology, and there were two microscope slides from each of those. There was an initial report done, and as I understand it, those results were sent to another consultant, Dr. Jim Anderson, who is a well known pathologist and biomaterials expert. I think Jim is in the audience, is that right?

DR. ZUPON: He is here, yes.

DR. BAUER: Jim, can I ask you a couple of questions about those?

DR. BOYAN: Dr. Bauer, I appreciate what you are trying to do, but I need to do something slightly different.

Your review is actually going deep into a discussion section that would entail us to do a slightly different agenda than what I had planned. If you would give me permission to do this, if we could go to the statistical reviewer, have them read the questions, and then take the break, because I can see how this is going. Unless you are going to really surprise me, it's going to go for a lot longer.

I think there are some of us who have been waiting. We are needing to break. So we are going to table this, Dr. Anderson, for right now, finish with the statistical review, and then we will have our FDA read the questions to us, take a break, and then come back to this. That will give everybody a chance to get caught up.

Maybe you could help them during the break, identify some of your spots for your questions, so they can start getting their answers ready.

Dr. Janosky?

DR. JANOSKY: Actually, in addition to the comments presented by Dr. Wilkinson and also the presentations by Dr. Bushar, I have four major concerns that would probably be best presented to the sponsor, with a chance for them to respond. So would you rather defer that also?

DR. BOYAN: Yes. Then let's go to the questions, and we'll just defer both of those. I want the questions now, so we can think about them on the break.

DR. LEE: Chairman and panel members, you have the panel questions on the back side of this draft. The previous one is just a draft. We just put together the final questions.

This is the summary of the presence of absence of statistically significant differences in U.S. and European studies. The European study was the pivotal study. In the European study there were statistically significant differences in diminution of fibrosis and weighted activity-related pain at six months in ADCON-L treated group compared with the control.

In the U.S. study there was a statistically significant difference in diminution of fibrosis at six months in the ADCON group compared with the control. There was no statistically significant difference in weighted activity-related pain at six months in the ADCON-L treated group compared to the control.

There was no statistical significance because at six months in ADCON-L treated group in the Roland-Morris activity performance scale compared to the control group.

Effectiveness and clinical utility; the primary efficacy measures was a scar score based on MRI. Patients MRI evaluations at 6 months and 12 months. Each scan had images obtained both before and after the injection of gadolinium DPTA.

Each MRI series consisted of five contiguous slides, called operative slides. It was cut through the middle of the disc space. The slice just cranial or cephalad was cut through the region closely approximating the location where the affected nerve roots sleeve separate from the long axis of the cauda equina thecal sac slice just caudal completed the area of the operated disc space.

The most cranial slice and most caudal slice overlapped the adjacent vertebral bodies and were used for visual orientation purpose. These two slices were not included in the scar analysis.

Each of the middle MRI slices was divided in four spatial quadrants centered on the thecal sac and were graded as follows. The independent academic neuroradiologist reviewed the films and assigned the scar score: Scar Score 0, no fibrosis of quadrant filled with scar; Scar Score 1, less than 0 percent or less than or equal to 25 percent of the quadrant filled with scar; Scar Score 2, less than 25

percent and less than or equal to 50 percent of the quadrant filled scar; Scar Score 3, less than 50 percent and less than or equal to 75 percent of quadrant filled with scar; Scar Score 4, less than 75 percent of the quadrant filled with scar.

If the patient has scar score 4 in any one of the 12 quadrants, it is defined as a scar score 4, extensive scar.

Question 1(a): Did the company establish the validity of the MRI technique for evaluating the extent of peridural fibrosis?

(b) The company provided an article, "Association Between Peridural Scar and Recurrent Radicular Pain After Lumbar Discectomy: Magnetic Resonance Evaluation," by Ross et al., Neurosurgery 38:855-861, 1996, which stated that the use of gadolinium enhanced MR in the evaluation of scar versus disc has been examined by a number of investigators, and the combined results give pre- and post-contrast MR 96 percent accuracy in differentiating scar from disc. references were cited to support this statement.

Do the PMA data establish that this MRI technique has adequate sensitivity to measure the extent of peridural fibrosis?

(c) On MRI findings in approximately 17 percent of the control patients and 19 percent of the ADCON-L treated patients scar scores changed by one grade between 6 months and 12 months. In approximately 5 percent of the control patients and 2 percent of the ADCON-L treated patients the scar score changed more than one grade from 6 to 12 months. Approximately 2 percent of the control patients had higher scar scores at 12 months than at 6 months (Amendment 6, pages 7424-7426), while none of the ADCON-L treated patients had higher scar scores at 12 months than 6 months. The company attributes the changes in scar score of more than one grade to some consolidation, remodeling or vascularization of the scar.

Can the change in MRI scores of peridural fibrosis in both groups between 6 months and 12 months be attributed to clinical changes, or is it possibly due to the MRI technique?

Question 2: The primary outcome criterion for the European study was the difference between the study groups in the extent of peridural fibrosis on MRI at the six month post-operative evaluation. Using the MRI technique, 38 percent of the ADCON-L treated group had extensive scar scores at six months, while 51 percent of the control

patients had extensive scar scores at six months.

In order to evaluate whether the 6 month data were predictive of outcome at 12 months, FDA asked the company to provide 12 month post-study surveillance data from the European study. At 12 months in 86 percent of the original patients, 28 percent of the ADCON-L treated patients had extensive scar scores (scar score 4), while 41 percent of the control patients had extensive scar score 4.

The secondary outcome criterion for the European study was the incidence of activity-related pain (ARP) while performing activities of daily living measured at six months post-operatively. The weighted activity-related pain (wARP) score was statistically significantly less at six months in the ADCON-L treated group, as compared to the control group, i.e., 1.24 and 1.58 respectively. This difference was not maintained at 12 months.

The primary outcome criterion for the U.S. study was the difference between the study groups in the extent of peridural fibrosis on MRI at the six month post-operative evaluation. Using the MRI technique, 54 percent of the ADCON-L treated group had extensive scar score, while 77 percent of control patients had extensive scar scores for the U.S. study at six months.

The secondary outcome criterion was the incidence of activity-related pain while performing activities of daily living measured at six months post-operatively. The U.S. study did not show a statistically significant difference in the mean weighted activity-related pain between ADCON-L treated and control groups at six month. Twelve month data are not yet available.

Do the PMA data demonstrate a clinical benefit?

Question 3. In the proposed label ADCON-L is indicated for use during lumbar surgical procedures, providing a temporary physical barrier to inhibit post-surgical peridural fibrosis. The protocol was for laminectomy (1.4 percent), laminotomy (16.3 percent), hemilaminectomy (40.8 percent), and hemilaminotomy (41.5 percent).

Can the PMA data be extrapolated to include a generalized use for lumbar surgical procedures?

DR. BOYAN: Thank you.

Now I would like to take the chairman's prerogative of eliminating lunch and working right through lunch so that we can move out of here. So what we are going to do, at 12:00 p.m. exactly we will reconvene here with Dr. Bauer's review, and then we will go to Dr. Janosky's review.

Then we will have the open panel discussion. So you have 12 minutes. That's it; 12.

[Brief recess.]

A F T E R N O O N S E S S I O N (12:06 p.m.)

MS. NASHMAN: While everybody is assembling, I just wanted to preface the general discussion. We're going to take this really slowly and carefully, because we want to be sure that the company has an adequate opportunity to respond. I think that Dr. Wilkinson's review was quite lengthy, and it is chocked full of stuff, and you now have a copy of that to go through.

So at the end of the three primary reviewers, I would like to give you an opportunity to not in the classic sense rebut, but to at least comment back before we go into a full fledged general discussion.

Dr. Bauer, you are on.

DR. BAUER: Again, I would like to resume by asking Dr. Anderson a couple of quick questions. My colleague, Dr. Wilkinson, has raised some concerns about basic biocompatibility. Jim, you looked at some of the histology, isn't that correct?

DR. ANDERSON: Yes.

DR. BAUER: Were you involved with the experimental design of either of these studies?

DR. ANDERSON: In part. Let me identify myself. My name is Jim Anderson. I'm a pathologist at Case Western

Reserve University, and I'm a consultant for Gliatech.

DR. BAUER: Did you do the gross dissection part?

DR. ANDERSON: I did not.

DR. BAUER: It seemed to me that whoever did the gross dissection was able to identify fibrosis, but in your histology report, if I interpret it correctly, you did not see any difference in fibrosis between the two groups? Is that right?

DR. ANDERSON: Between which two groups?

DR. BAUER: Between the ADCON-L groups group and either the sham or the other controls. In other words, you did not see a reduction in fibrosis in the ADCON-L group?

DR. ANDERSON: I think it has to do with the way that the numbers were compiled. I think there was a reduction in fibrosis. You have to remember when you are looking at something grossly, you really are only looking at two planes. You look at two planes when you look at something histologically, because you are looking at a cross-section.

There was no doubt that the, if you will, density of fibrosis was much less in the ADCON-L for example, as compared to the sham.

DR. BAUER: Histologically, you mean?

DR. ANDERSON: Histologically, yes; many more fiberblasts, much more collagen, whereas the ADCON materials had what I would call an early granulation tissue type of collagenous appearance. Perhaps it has been described as more wheeler(?), perhaps higher density of glycose amino glycans that were present in it.

DR. BAUER: Maybe I had just gotten the abbreviated version of your report. I hadn't appreciated that from your descriptions that were given to us.

Again, that wasn't really quantified, is that right in any kind of way? The gross dissection was, but in terms of the histology, was there any kind of quantitation that could be used in a statistical study?

DR. ANDERSON: I used what we commonly use as a subjective scale, 0 to plus 4, and evaluated what I consider to be dense fibro-connected tissue. I also evaluated granulation tissue. Since these studies were mainly directed at the safety aspects, we were greatly concerned with the presence and persistence of acute and chronic inflammation, necrosis, and possibly abscess formation.

DR. BAUER: The gross dissection did not describe the presence of any cysts in any of the experimental groups, but in your histology you identified some cysts in both the

ADCON-L, as well as a number of the other control arms. These were attributed to basically the operative technique. That is your interpretation, I take it?

DR. ANDERSON: Yes.

DR. BAUER: Again, they weren't interpreted grossly. Were these big enough that they could have been seen by the gross dissection?

DR. ANDERSON: I really doubt it. I think these were micro cysts. As you know, once we get granulation tissue and fibrotic changes that start to occur around let's say materials which will eventually disappear, as this material did, and even the control materials did, we are left with that cystic space, and that's what it was simply. It wasn't filled with blood. It was probably filled with just perhaps extra cellular fluid. There was no indication that it really was any form of pathology. It was simply a microscopic cystic space.

DR. BAUER: Again, Dr. Wilkinson had expressed some concerns about basic biocompatibility. You have done a lot of studies looking at inflammatory reactions to biomaterials. Are you concerned about biocompatibility from this product?

DR. ANDERSON: Not at all. This product is very

similar to what I have seen in the past with high uranic acid. If the material let's say were present in submicroscopic amounts, that is to say, something that could not be identified under the microscope, and it had let's say elements that would raise into question, issues of compatibility, I certainly would expect to see for example, macrophage activation, perhaps some other cellular indicators that there might be biological activity there; I didn't see it.

I am convinced that the material is gone in four weeks. If there is material there, it is not creating a biological effect.

DR. BAUER: Thank you.

DR. ANDERSON: Thank you.

DR. BAUER: In conclusion, I don't have any further questions, but in my own conclusion of the pre-clinical studies I would also agree that I think the product is safe. Evidence of its efficacy is, I think, pretty weak based on the animal studies, but I will acknowledge that it is very difficult to create an animal model that would allow a good quantitative measure of this fibrosis, and that that just may intrinsically be a problem of animal models and experimental design.

DR. BOYAN: Thank you very much. Dr. Janosky.

DR. JANOSKY: In addition to the issues that Dr. Wilkinson has raised, and also that Dr. Bushar had raised, I have about let's say five issues that I think are crucial to the application in evaluating reasonable assurance for safety and effectiveness, and I was hoping to walk through those rather quickly if we possibly can, but delving into the seriousness of each one of these issues that I would like to raise.

My understanding is that there was only one neuroradiologist that evaluated each of the patients for scarring. Is that correct?

DR. SILKAITIS: That's correct.

DR. JANOSKY: So given that position, what are some data that is going to convince me that this neuroradiologist was reliable, both within themselves, and also compared to other neuroradiologists?

DR. SILKAITIS: There was a validation report that was submitted with the PMA that reviewed that interreader variability. The kappa was I believe 0.6.

DR. JANOSKY: Right, that's the issue that I'm getting at. I would consider that to be a very low reliability.

DR. SILKAITIS: It's my understanding that that is a moderate reliability.

DR. JANOSKY: A kappa of 0.6?

DR. SILKAITIS: I'm sorry, it was 0.68.

DR. JANOSKY: Still, you are talking about approximately 30 percent of the time, not having agreement. If we go with that piece of information, then if I look at those score changes from 6 months to 12 months, and some of those score changes that we are looking at, you are actually seeing that the scarring is getting better, and that's one of the issues that we were dealing with today, trying to figure out why that was happening.

Why would you not attribute that to unreliability within this neuroradiologist, given especially that the kappa is 0.7?

DR. ROSS: Maybe the best way to answer your question if I may, is to show a couple of images, particularly of the scar score changes; a dramatic change.

DR. JANOSKY: If time permits.

DR. ROSS: Particularly with the changes in the scar score, this, for the most part, not a subtle change. This is the 6 and the 12 month image, sort of ancillary findings; just nice slice position correlation. You can see

the positioning of the vertebral body here, this sort of wing configuration, which is precisely reproduced on the 12 month data. Here is the basie(?) vertebral lane going through the vertebral body. You see the exact slice position here.

Now what you were asking about is the change in scar score, so we have really a slice that looks identical from the 6 to the 12 month time point. Here is the thecal sac. Here is the facet. Here is the soft tissue, the scar, which is present along the dorsal aspect. Here it is at 6 months. At 12 months this now shows fat signal intensity.

These type of changes from 6 to 12 months -- could it be reader problem? Could it be machine problem? You think of all these things, but certainly the slice positions were very good going from 6 to 12 months, and nothing suggests that I am changing my scar reading going from either the European study or the U.S. or the 6 to 12, particularly in light of these really dramatic changes I think you see on the images.

DR. WILKINSON: These are images through the vertebral body. I think you did not include those in your statistical analysis, is that correct?

DR. ROSS: They were taken one slice -- this is

angled down low, so these were obtained and non-angled. So when you come down low, you are going to cut through some vertebral body before you get to the disc when it is angled. So the three slices were utilized at the level of the laminectomy site, and then one slice above and below. I scored five levels above and below as well. So really, it encompasses the whole level. So this is sort of at the bottom of that range.

DR. MC KINLEY: I would like to add a comment. That is that at both 6 months and 12 months, despite the fact that there was a small decrease in about 20 percent of the scar scores, that the decrease was the same in both the ADCON and control groups. The scar benefit, which is what we are here to discuss, was statistically significantly maintained at both the 6 and 12 month time points.

DR. JANOSKY: I would like to pick up that in a second, but I want to continue on this point, just for one more quick question. Given the cases that were used for the data within this application, was there an estimate of reliability done both in the U.S. study and the European study? So does that value of 0.67, is that using the cases within this current application?

DR. SILKAITIS: That report that was submitted was

from the pivotal European trial, and re-reading of those images.

DR. JANOSKY: But it was not also calculated for the U.S. study? So you don't have an independent assessment of reliability for the U.S. readings also?

DR. SILKAITIS: Right, well, because the same individual is used for both studies, it was thought that that one report would be adequate.

DR. JANOSKY: Let's just continual along the line that was raised, but deal with it a little differently. If I look at the U.S. study, there is a high number of non-evaluable subjects. Actually, about 47 percent are evaluable. I understand how some of the assessments are not done given the pain was not there. I don't see a comparison that looks at baseline characteristics of those that were evaluable and those that were not. Did you do such an analysis?

So if I look at the individuals that reported no pain, so then did not go on to get the wARP, what are the baseline comparisons of those individuals? So are they selecting themselves, and that is leading to some bias or not?

DR. SILKAITIS: You are referring to the pivotal

study?

DR. JANOSKY: The U.S. study.

DR. SILKAITIS: The U.S. study had one time point.

DR. JANOSKY: The six month time point.

DR. SILKAITIS: Right. Could you repeat your question?

DR. JANOSKY: Sure. If I look at the number of evaluable subjects from that study, it is approximately 74 percent.

DR. SILKAITIS: Right.

DR. JANOSKY: I understand how that number is being obtained. Some data were just not obtainable; for some of the assessments they were not done. If I take a look at the data let's say from the wARP, that was only administered to a patient who reported pain, is that correct?

DR. SILKAITIS: That's correct.

DR. JANOSKY: So now if I take a look at the baseline characteristics of those subjects that did get the wARP and those that did not get it, that would give me an assessment of whether those subjects reporting no pain are actually different in some other way, to get into this issue of biasness in terms of evaluable and non-evaluable

patients.

DR. SILKAITIS: In terms of the evaluation of the activity-related pain score, the weighted score, pre-operatively, yes, we did compare the treatment groups of the evaluable group. I think we have the all patients also; everybody that we had at that time, and as it was shown earlier, it was not statistically significant.

DR. JANOSKY: I'm not interested in the treated versus the control. I'm interested in those responding no, I did not have pain versus those who responded, yes, I did, who then went on to get this additional assessment.

DR. SILKAITIS: Right, we did do that analysis I think, but I don't have it available right now.

DR. JANOSKY: Can you recall what the outcome was of that analysis, just in a general sense?

DR. MC KINLEY: I just wanted to reiterate that for the U.S. study, this is an interim report. The reason that the drop outs are a little higher than what you might expect with a final study is the fact that there were still several patients that had not completed either MR assessments are clinical assessments, but at the time point that the interim report was chosen, that we had to freeze the database at some point.

So I think it is a little difficult to talk about drop out rates and things of that nature, with an interim analysis.

DR. JANOSKY: You always present to me a wonderful lead in to the next question, but I'm going to resist and just go back to this question again. I started this off by saying I understand how that value was obtained in that 74 percent is low, but given the point at which you are in that in protocol, part of it understandable.

I'm having a problem with not administering that wARP, and I also think Dr. Wilkinson had mentioned something very similar. I want to get at whether that presented a bias or did not present a bias. So that is the issue that I'm concerned with now.

DR. MC KINLEY: Let me just comment on the wARP assessments in the pivotal trial, because we did do an analysis were we considered all patients. Those patients that had zero pain or no pain were included in the analysis. Dr. Bushar did present that particular analysis. We do encompass the patients with no pain into the entire wARP analysis. The benefit was maintained. It was statistically significant 2-tailed analysis.

DR. JANOSKY: Assuming that those were in that

categorization, but I'm talking about baseline characteristics, whether they were different to begin with. If you are presenting at some point, and saying you are not having pain, were you different in some way when you started? If you don't have the analyses --

This will pretty much be the final question, with maybe a subset if you lead me in that direction. This is again, follow-up to what you had said earlier. If I look at the results obtained from the European study and the results obtained from the U.S. study, and I do understand that these are different populations. I understand that they are happening at different time periods, both in the assessment, and when the study is conducted.

I see in terms of safety, that for the most part those studies are the same, the results of the study. That gives me some assurance that these are comparable studies - some assurance. Then when I look at the effectiveness data, I see very different outcomes in terms of the high level of scarring that is reported in both groups.

That leads me back to that issue of reliability, as well as perhaps some surgical differences, whether it is surgeon, whether it is technique, whatever it might be. If you could answer a little bit about sort of what I'm seeing.

DR. SILKAITIS: As a matter of fact, we do have some answers to those questions. Dr. Robertson would like to make a comment, and like to share a slide that explains that to you.

DR. ROBERTSON: Jim Robertson, Professor of Neurosurgery.

If you will notice in the European and the United States study there was at twice as many people had true, extruded fragments of disc as the European study. There is a host of literature, particularly in The Journal of Spine in the last year that shows the intense inflammatory reaction that occurs around the free extruded fragment.

Other than that explanation as the increase in the incidence of scar that was seen, we don't have any, but that's a very logical explanation, rather than any surgical technique or any other thing that we could think of.

DR. MC KINLEY: I'd like to share the data with you. As you can see on the slide that is currently projected, if you look at the disc pathology, as Dr. Robertson pointed out, between the U.S. and pivotal studies, we said that in the United States we did observe more severe disc pathology, and this is what we attribute, at least in part, if not totally for the difference in scar scores. So

that is the data.

DR. JANOSKY: So you would argue the patient populations are different then to some extent? Okay.

As the final question, I see some of the statistical tests are done 1-tailed or directional or non-directional tests, and some of course are done 2-tailed. So if we think of them as directional or non-directional, I'm a little confused. Why are you reporting some of the results as 1-tailed, and some of the results as 2-tailed, where if I would just treat them all as 2-tailed or 1-tailed, I would clearly come to different conclusions that were made?

Also, for your interim analyses, why were the P values not adjusted.

DR. MC KINLEY: I'm sorry, I didn't understand the last question. I can answer the former.

DR. JANOSKY: For the U.S. study that is considered as an interim analysis, why were the P values not adjusted? So within that study, not only is the issue of directional and non-directional a problem, but also you didn't adjust the P values given the fact that that was an interim analysis.

DR. MC KINLEY: Let's answer the first one. Let me just give you a few points, and then I'm going to have

Phil Lavin, our statistician, talk in more detail about the second one.

DR. LAVIN: My name is Phil Lavin. I'm with Boston Biostatistics, and I'm a paid consultant to Gliatech.

One of the issues that we had in this trial was the issue of 1-sided versus 2-sided tests. If you look in the original protocol, the European trial, you will see some mention of both 1-sided and 2-sided testing in there.

You will also see if you look at pre-clinical animal data in terms of adhesions, that there was some good evidence there for thinking about 1-sided testing, which is why the company, when they launched the European trial, went in that direction.

You will also see that in the U.S.A. trial, there was a considerable amount of desire to go with the 1-sided test, because that's what other sponsors were doing who were presenting to the agency, and there was also a desire to keep the results consistent in the PMA filing. So the 1-sided testing methodology was selected.

As your statistician and others can tell you, the simple way of just handling a 1-sided to 2-sided P value conversion is to just double the P value from the 1-sided test to get the 2-sided number. So those are the rationales

for thinking about 1-sided versus 2 sided.

Now another question that was just raised was the issue about adjustment of the P value for doing an interim look. Now I consider that to be something that should have been in the protocol when it was originally written, but there was no Landemette's(?) calculation in there for doing the P value calculation.

If I were making a recommendation at the time, I might have tried to put in there some type of a boundary stopping wall, but for whatever purposes there were, there was not really any P value calculation adjustment put forth.

Instead what I would like to propose, which is what is done for a lot of agency trials in this situation, is that you do the final P value calculation at the end, and so you might require in a situation like this where you looked at the trial, not with the point of view of stopping it, but from the point of view of trying to see where you are at, to require a P value through this Landemette's calculation.

So that would probably amount to about a P value of 0.045 required for significance when you get to the end, just from my experience with trials like this, of this sample size.

DR. JANOSKY: I just need to follow-up rather quickly. Dr. Bushar had given us some analyses and presented them today, and those are done with the 2-tailed P value. If I look at some of the other analyses that were presented, it's still 2-tailed. So which one should I follow? Because again, I'm going to come to different conclusions on some of your outcomes, depending upon what I use.

DR. LAVIN: Let's be very specific here. With the U.S.A. trial I believe that the study clearly states, and the protocol clearly states that 1-sided testing was to be the approach. That is exactly what Dr. Bushar put into his overhead. That came from the protocol. Also Dr. Lee mentioned that as well. So I believe the 1-sided testing is the way to go with the U.S.A. trial.

I also believe for the sake of consistency, and the strength of the animal studies as well, that really you should go with 1-sided testing. So I would like to put forth my opinion that 1-sided testing would be the most appropriate here, given the way the protocol hypotheses were constructed, given the way that the study was powered, and given the way that others have presented the data.

DR. JANOSKY: I think I'll conclude at this time.

DR. BOYAN: All right, thank you very much to all the reviewers. I now would like to give an opportunity if you would like to make any specific comments in response to Dr. Wilkinson's review, and ask that you go to the podium for that.

DR. SILKAITIS: Thank you, Dr. Boyan. Yes, we would like to respond to Dr. Wilkinson's comments. We will have people go to the podium to respond to them.

DR. MC KINLEY: I'm going to have Fredd Gisler(?) talk to the issue of the -- Dr. Hardy is going to talk to the issue of free fat grafting.

DR. HARDY: I think the operant word when you talk about standard of care is not whether standard of care -- the word "de facto" I think was used in the submission. The fact is that while some surgeons do in fact use free fat grafts to hopefully prevent epidural fibrosis, free fat grafts have never been subjected to any kind of a controlled, double-blind study to see if they are effective.

In fact, a great many neurosurgeons and orthopaedic surgeons don't believe that they are effective. Also in fact, a lot of neurosurgeons and orthopaedic surgeons don't use them. So that while de facto it may be a standard of care, it really isn't a widely accepted standard

of care.

Furthermore, it really is technically different than putting gel in and around the nerve root, because all you really do when you put a free fat graft on is lay it on the operative field, and that is it. It doesn't surround the nerve root. It doesn't act in the same way that ADCON did.

So for this reason, and also some people use fat grafts with other medications and so forth. So that it seemed most appropriate to use as a control standard operative technique, which is to do the operation and close, and not a free fat graft, which is not a widely used or not universally used technique.

DR. WILKINSON: I certainly agree with my eminent colleague that this is not an accepted, widely, and universally accepted operative technique, however, the manufacturer and presenter both today used the term "standard treatment."

I also would disagree with Dr. Hardy that everybody simply throws the fat on top. I make a great effort of putting the fat back where I took the fat out of, and I put the fat graft ventral and lateral to the nerve root at the time I replace fat.

So there is tremendous variation in how this other technique is used. It has not been standardized and subjected to this kind of rigorous analysis. But if a manufacturer is going to declare it a standard treatment, that becomes significant for this PMA.

DR. MC KINLEY: I'd like to now address the issue of the correlation between recurrent radicular pain and scar.

DR. BOYAN: And the volunteer is?

DR. ROSS: Jeff Ross. I guess one thing is that the point of the paper was derived from the European data. If I could be very simplistic, it said the point of the paper is scar is shown to be bad, taking that large group of patients. Now of course the problem is how do you define that in any one patient? You can't.

Because this was the combined data from both the ADCON and the control group, taking them together you get enough -- and statisticians can speak about -- but the numbers are large enough that we can talk about scar being bad at that point. When it gets broken down into ADCON and control by themselves, we don't have that significance.

The other point I want to make, which again is minor and I don't want to belabor it, but the comments at

the end of the paper, I do apologize for not giving those to the panel. It wasn't exactly part of the paper per se, but again point out that there were some kind comments about the paper back there as well. So it wasn't an obfuscation of data by not submitting those.

DR. BOYAN: Thank you.

DR. MC KINLEY: I would like to add one more thing to the association between scar and pain, and that was an additional analysis that was specified in the protocol, and submitted in the PMA, and that was between scar and wARP or activity-related pain. We performed that analysis.

So on your slide behind you, as you see on the right, not only as we previously discussed was there the significant association between scar and recurrent radicular pain, but we also did another statistical analysis for both ADCON and control patients. We found that there was a significant association between extensive scar and change in activity-related pain when in this particular analysis. So basically pains with more scar, regardless of their treatment group, also had more activity-related pain.

DR. ROSS: I did also want to make a point about the question of extent of scar correlating with density on MR. That is a fascinating area, and I have a lot of

theories about it, but there is no hard data to present on that, because really given the limits of our technology and the state-of-the-art technology we used, when you look at it, I can't say anything other than sort of binary approach, is there scar or isn't there scar?

We don't have the technology to say really go to histologic level and say, what is the amount of collagen tissue at that point. That just doesn't exist.

DR. SILKAITIS: I would also want to clarify for the panel members that everybody in the study -- no one had fat graft.

DR. MC KINLEY: I wanted to add a comment concerning the distribution of scar scores. I would like to make a couple of comments, the first being that in the pivotal study at both 6 and 12 months, and in the interim results of the U.S. study if you look at the overall distribution of scar scores regardless of how you categorize it, that difference is significant.

We found through the correlations between scar and clinical outcome that it is the most extensive scar that is most highly associated with clinical outcome. So we feel that it we should then focus on extensive scar, but regardless of how you segment the data, the ADCON group had

a benefit.

DR. BOYAN: If there are no additional comments, I think what we should do next is move to the general discussion. Members of the panel can still call on you, but at this point you are back to the audience. I have the official wording here is that you are to remember that you are now public observers at the meeting.

I would like to remind the public observers at this meeting that while this portion of the meeting is open to the public observation, public attendees may not participate, except at the specific request of the panel. That means that we ask you the questions, and you come forward. So you guys are actually free from this moment to go back and sit comfortably in the audience.

DR. WITTEN: Are moving towards discussion now?

DR. BOYAN: Yes, general discussion.

DR. WITTEN: Have the finished?

DR. BOYAN: They are finished. I just instructed by my colleague to my immediate left that I was to send them back to the audience. Do you want to let them stay comfortable there as part of the audience? Okay, we're going to let you sit at that table as to be comfortably part of the audience. Wherever you want to sit, sit, but you are

audience now.

**Agenda Item: Panel Discussion**

DR. BOYAN: Now for the general discussion we are going to go around the room, and we're going to start with Ms. Domescus, and let each of the members of the panel ask one or two questions that are the ones that they consider to be the most important to their particular area of interest to get a general discussion going.

You can feel free to ask other panel members questions, anybody in the FDA questions, or anybody from the company questions.

MS. DOMECUS: I actually don't have any specific questions for the sponsor. I guess I have a general question to the panel, which may become evident as we go around the table. I have heard a lot of debate this morning about the significance of scars as it relates to pain, but I haven't heard a lot of discussion about scarring at it relates to the ease of reoperation, and all the risks attendant with that. That would seem to me to be an undebatable clinical benefit, but I wanted to hear some comments on that.

DR. WILKINSON: Well, I think you have probably heard too much from me already. One question, and I suppose

it's pre-clinical studies. In clinical use, gelatin foam tends to swell. For instance if it is left under optic nerve by spinal fluid, it can swell over a period of days and cause visual loss. If it's in the epidural space and is soaked in blood, it can swell and change size.

This material is made up largely of gelatin foam. Does it change volume over time when it is left in the epidural space or around the nerve?

DR. SILKAITIS: I will defer the answer to Dr. Zupon.

DR. ZUPON: Basically, your comment is correct if you are dealing with non-fully hydrated gelatin. Our product though, definitely the gelatin that is inside the product is fully hydrated. There is no more absorption of water into our product at all, so there is no swelling characteristic.

DR. WILKINSON: A comment that I was pleased to hear Dr. Ross confirm that there is at present, no known and proven correlation between MRI appearance of extent of scar, and MRI appearance of density of scar, which is the factor that Ms. Domescus was asking about, the ease of reoperation. Is that scar dense scar? Having reoperated on many patients with MRI appearance of epidural scar, I have been pleased to

find that the scar is very filmy, and very easily opened.

DR. LAURENCIN: Going over the statistics, the question is what will your final claim be? Certainly I guess you are going to push very hard in terms of having a claim for decreasing fibrosis, and you may have some points in that area.

The whole question about the ADCON being able to relieve pain becomes very much up in the air in terms of in looking at the statistics and looking at the fact that there was some pain relief at 6 months in terms of activity-related in European study, but not at 12 months. Also in the U.S. study there was a problem in terms of getting meaningful relief of pain.

Would you want your package insert to say relief of scar and relief of pain? If so, how can you make claims in terms of relief of pain when you have data from two different studies, which makes it difficult to substantiate it?

DR. MC KINLEY: Yes, I do agree with your first comment that we do have data to support the reduction of scar or fibrosis. As it relates to pain, in the pivotal study, it's the basis of our PMA submission. Everything else is supplementary in support of that.

In the pivotal study we did clearly demonstrate that ADCON patients had less activity-related pain. Now that value was not carried forward to 12 months. The difference was maintained, the relative trend was maintained, but due to the fact that we had some drop out of patients, and that the fact that the study was designed as a six month pivotal study.

It wasn't designed necessarily to demonstrate activity-related pain significance at 12 months, which is a different power calculation. I guess a statistician would agree that if the end were larger, at some point we would have achieved that statistical significance.

There is a third point that I would like to make, and that is at the 12 month time point, with the natural portion of disease you begin to see some recurrence of symptoms. That also may begin to affect the pain measurements at 12 months. I would like Dr. Spencer to add a comment on that.

DR. SPENCER: When you are doing a study such as this where you are evaluating the surgical results for sciatic disc herniations, as you follow these patients out, pretty soon you start documenting the natural history of the underlying disease, rather than the treatment you have

initiated. In other words, these patients all had degenerative disc problems which predisposed them to herniation in the first place.

So as you carry them out, pretty soon the effects of your treatment are overshadowed by the natural history of the disease process in the first place.

DR. LAURENCIN: So are you saying that because of confounding variables, that it cannot show efficacy in ADCON after six months?

DR. SPENCER: I'm just saying that it's my opinion that one of the explanations for why the statistical efficacy trails off after six months is that it may be that we are documenting the natural history of an underlying condition, rather than the treatment effect itself.

MS. DOMECUS: I wanted to point out something too in looking at the numbers. Even though we are making a big deal about statistical significance. If you look at the 6 month scores, in ADCON it is 1.24, and at 12 months it is 1.32 versus the control is 1.58 versus 1.59. So even though it's not statistically significant at 12 months, numerically it seems to be a really minor difference.

DR. MC KINLEY: It's important to remember two things about the activity-related pain measurement. First

of all, the scale was 3.2. The activity-related pain measurement analysis had two components, a mean component and looking at individual activities. The scale was 3.2. So if you look on an absolute basis, the difference at 6 months was around 15 percent, and still over 10 percent difference on that relatively small scale at 12 months.

Probably more important clinically is that you need to look at the individual activities. When you look at the individual activities, all of the ADCON patients did better in each of the activity requirements, and some as much as 40 percent better.

DR. LAURENCIN: Just a final question. Basically for the clinicians who are in working in some way with the company, if a patient came to you and said, I'm looking at whether I should have the ADCON placed in me or not, a year from now, doctor, would you say that if I have this placed, will my pain be improved? What would you be able to say to them?

DR. SPENCER: One of the most frequently asked questions to me when propose a laminectomy discectomy for surgery is the patient says, well, doctor, what about the scar tissue that is going to be there after surgery, is that going to be symptomatic? Is that going to cause a problem?

I tell them a scar is an inevitable consequence of surgery. I do everything in my power to minimize it, but I can't predict one way or the other.

So I think if there is a product available that reduces scar tissue. When a patient comes to me, I will tell them that I would like to use this material, because it reduces the scar tissue, and I think it reduces the probability that they may have problems down the line from scar tissue as a result of the surgery that I'm performing.

DR. LAURENCIN: But based on the data, what would you say to them? If you they say, what's the data on this in terms of --

DR. SPENCER: That it reduces the peridural scar tissue.

DR. LAURENCIN: But in terms of pain?

DR. LAVIN: I would like to add something to the discussion regarding this clinical utility measure. This is something that has been with the device part of the agency for 15, 20 years. One of the things that we did to help try to understand what is the clinical utility of ADCON versus control, we made an overhead.

Now what we did to look at this measure is we decided to take all of the clinical information which was

available to us. We took the MRI scar score, and we also had the wARP, the ARP, the SLR, the lower back pain, and the Roland-Morris. We looked at it separately for the European trial, and also for the U.S.A. study.

One of the things that we required was we looked at what percentage of the patients at six months will have a non-extensive MRI scar score, and will have an improvement in the wARP, an improvement in the other back pain measures. For the European trial at six months, requiring all of these to be in place. Forty-six percent of the ADCON patients met those criteria.

This was being as conservative as possible, holding aside the patients with missing, and not counting them in this analysis. So this is a worst case analysis. So 46 percent of the ADCON patients at six months in the European trial versus 28 percent of controls met this criteria of everything improving and the MRI scar score being not extensive. The 2-sided P value for that was 0.004.

Now taking the data out to 12 months, where admitted we had a small loss of patients, it had actually risen to 52 percent improvement with all these measures improved for the ADCON patients --

DR. WITTEN: Excuse me, I don't think we've seen this analysis. Was this analysis provided in the PMA?

DR. LAVIN: This analysis was not provided in the PMA. It is in response to the question of what's the clinical utility.

DR. LAURENCIN: The question isn't regarding clinical utility. The question is hopefully a simple question regarding pain at one year. If a patient comes and asks will I have pain in one year, based on the data that you have, what is the likelihood of my having less pain because I had this implant placed, what would be said? Not clinical utility in terms of scar, because that takes into account scar and other levels of scar.

It's not levels of scar. I think the question is in terms of levels of pain. At six months we have some data that says there is improvement. At 12 months it sounds like we don't, and I'm trying to get a sense for whether the sponsors believe that or they don't.

DR. LAVIN: Well, I've looked at that data as well. Although this is not in the PMA, it is about 80 percent for the ADCON group, versus about 65 percent for the controls. That is just if you take away the MRI scar score and look at those other measures, which are pain related.

So you are seeing a 15 percent or better advantage for ADCON at 12 months. Also you are seeing it at 6 months as well, so it has legs.

DR. LAURENCIN: A statistically significant difference at 12 months?

DR. LAVIN: At 12 months? I have not calculated that yet, but I would assume that at 15 percent, it is going to be darn close.

DR. WITTEN: I would like to remind the panel that in their deliberations they need to consider the data that was provided in the PMA.

DR. BOYAN: Thank you, Dr. Witten. Dr. Janosky, any further questions?

DR. JANOSKY: Just a quick follow-up to one of the questions I asked before and presented to the sponsor, as a comment that clinical utility that was just presented, I realize it was not in the PMA, but was done by a 2-sided P value. So going back to what you said before, that everything that was 1-sided again, was not what was going on.

If I look at the unreliability again, I still can't get off that issue that kappa being just less than 0.7. What type of errors are you seeing then? Which ways

were the errors occurring? So if agreement is 0.7, then a fair amount of the cases are not in agreement upon retesting or upon looking at the scan at the same, which way are the errors occurring? Are you recording things as more severe than they actually are? Or are the errors occurring the other way?

I can't remember the gentleman's name before, but I think the neuroradiologist had spoken to this before.

DR. ROSS: In general, the errors were occurring in the central portion of the scoring. If it is 50 versus 51 percent, is it a 2 or a 3? Those are a little more problematic than a score at the 1 or the 4. If the whole quadrant is done, it is an easy call. If it is at the other end, where there is a tiny amount, it's an easy call. It is in between where there is a shift.

DR. JANOSKY: So that's the non-extensive part then, when you categorize that?

DR. ROSS: Correct.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: I have three items to discuss, two of which will be questions, and one will be a comment. The first is with respect to pre-clinical. Please elucidate for me on the pre-clinical studies. I saw a video that showed a

difference in the dissection on reoperation between animals that had no barrier placed, and animals that has ADCON-L placed. Was that a single or two case analysis, or the was the ease of re-exposure of the dura evaluated systematically in the animal study? Can somebody speak to that?

DR. ZUPON: Can you clarify the question for me a little bit?

DR. YASZEMSKI: Okay, I'll try. I'll try to say it again. I saw a video that showed an example of an animal getting reoperated.

DR. ZUPON: No, that was not a video. The video you saw was a human video.

DR. YASZEMSKI: Oh, okay, so there was a human being reoperated. Thank you.

The reoperation is the point I'd like to speak to. In the animal study, was any assessment of ease of reoperation made, so that we could know whether this is a very common finding that with the ADCON-L it is very easy to re-expose the dura versus the control cases?

DR. ZUPON: In the pre-clinical there was a very formal scale of going down various layers, layers of skin, going through the muscle layers, down to the dura of attempting to get the -- the evaluators were blinded, and

they were making notes about how thick or tenacious the scar was that surrounded the dura.

DR. YASZEMSKI: Please remind me, what were their conclusions?

DR. ZUPON: The conclusion was that the ADCON-L very, very significantly, P was 0.0001 reduced peridural scar compared to the control animal channel operations for any of its components.

DR. YASZEMSKI: Thank you.

My second question, I will ask for comment on this from either the panel or the FDA or the sponsor's statistician. As I was reading through it, I saw that the six month data included 71 percent of the patients. Is that accurate? Is that a high enough number of those randomized to be okay?

DR. MC KINLEY: Was that the U.S. study?

DR. YASZEMSKI: I don't remember which study that was.

DR. MC KINLEY: Let me just make a comment that in the European pivotal trial the drop out was about 10 percent on average. About 90 percent of the patients had follow-ups, so that is probably the U.S. study. Again, that was an interim analysis, and the reason for that higher rate was

due to the fact that we had a lot of patients who either had not come back for MRIs, or not had data entered into the database by the cut off date.

DR. YASZEMSKI: Thank you.

My last is simply a comment. My comment is that we have discussed before the issue of the control group being no treatment at all. I would submit that a not insignificant number of us do put something over the dura after exposing it. I think the common somethings are fat or a gelatin sponge. It would have been really nice for me to see a comparison that contained either one or both of those as comparison groups.

DR. ZUPON: In the animal studies we did do that comparison, comparing ADCON-L against both of its primary parts, which is an absorbable gel from USP and the polyglycan ester. Again, there was no statistical difference between sham operations, absorbable gelatin, or the polyglycan ester among peridural scar. In all situations, the ADCON-L was statistically -- reduction of scar compared to all three of those in both the rat and the rabbit studies.

DR. YASZEMSKI: Thank you.

DR. BOYAN: I'm going to ask a couple of brief

questions, and actually I wanted to be sure that they are understood that in the context of a positive context. I'm asking just informationally for myself.

In the material that I had, it wasn't always immediately clear to me where the original products came from. I don't mean what vendor; I mean the derivation. One of the hypotheses I have for why you are getting this reduction in scar is that you using a porcine product, which is in fact going to encourage a greater degree of resorption than maybe it was a human collagen than it might. So that on the one side is very positive.

On the other side, you do run the risk of a delayed hypersensitivity reaction in some small group of patients that will become sensitive.

The other component in there is the polyglycan sulfate, which I wasn't quite certain whether that was biotechnologically derived. In the course of the discussion the concern about endotoxin is if it comes from biotechnology, there is an endotoxin component, which at your level is quite small, and may also contribute to the increased resorption of your material. Potentially of other scar that is forming might be resorbed because of this enhanced immune response. Is it a biotechnology-derived

product?

DR. ZUPON: The polyglycan ester is not biotechnology-derived.

DR. BOYAN: It's not, it's a synthetic?

DR. ZUPON: It's a synthetic process, and is not a high source of any endotoxins.

DR. BOYAN: Okay, so resolves a whole concern I had. Actually, I thought it was a clever way to bring an insult to the site, but so much for that plan.

So my next question is that I did notice in your data, and I noted also that it doesn't affect the clinical outcomes, but there is an increased amount of adhesion formation in the dorsal segment in your ADCON-treated human compared to the control-treated humans. I wondered if you had any thoughts on that?

DR. MC KINLEY: I assume you are commenting on the reoperation observations?

DR. BOYAN: Yes.

DR. MC KINLEY: I would just make a comment that the ends for those observations were relatively small.

DR. BOYAN: I agree.

DR. MC KINLEY: I would like to have maybe Dr. Hardy or Dr. Gisler add an additional comment as to why, but

we don't attribute that to any product-related observation.

DR. HARDY: There is always the possibility when you are dealing with a handful of patients that a little of the product might get moved inadvertently by a sucker as you are closing, or that it might run down. So I think to draw any really firm conclusions from that site particularly is going to be fairly difficult.

DR. BOYAN: Too soon for that?

DR. HARDY: Yes.

DR. BOYAN: Okay, thank you. Dr. Hale.

DR. HALE: I just have one question for the sponsor, going back to the issue of validation of the MRI data for assessment of scars. Either in the human reoperation data set or the animals, if that data was available, was there any attempt made to correlate your interoperative findings with the MRI data?

DR. HARDY: It is very difficult to make that kind of analysis, because the reason the patients were reoperated is that they had something like a recurrent herniated disc, so that you are comparing apples to oranges. I think this also applies to the question that was raised earlier about comparing pre-operative amounts of scar tissue. You've got a herniated disc there, and that is going to distort all of

your observations.

DR. MC KINLEY: We did have some anecdotal analysis on a few patients that corresponding MRs. We found that the correlations were good.

DR. HALE: I realize it's a small data set, but it seemed like that might provide you at least a little bit of validation for the technique, but given the nature of those reoperations, that may not have been that good of data to present anyway.

DR. ROSS: Also, a fair number of those reoperations were early on after the initial surgery, making the numbers even smaller. So in that very early time point, the diagnosis of what is scar or what is recurrent herniation is problematic. You need to be out farther.

DR. HACKNEY: I was asked to comment on the MR features of this. Although we have touched on that before, maybe I will anticipate some of the panels, at least with my opinion of the MR. First of all, it doesn't surprise me at all that some of the scar score changed over time.

If you read MRs on people who have had back surgery, and even people who haven't who have degenerative disc disease, you see scarring in the epidural space. Sometimes it gets better; sometimes it gets worse. I

suppose I would have been surprised if in such a large number of patients, no one's scar score did change. That is an expected finding.

We are asked whether the MR technique is reliable for quantitating the scars. There is abundant evidence that MR is excellent for telling the presence of scar and its location. That is why it is used for this purpose clinically on a routine basis. That has been well established for a number of years, and I don't think there is any debate about it.

The manufacturer's attempt to measure the extent of scar is something that has not been done very much. I think the data they have is essentially all the data there is about how reliable it is for measuring the extent of scar. I don't think we are left only with the data they present.

We are left with the fact that we know MR, as a technique, gives exquisite anatomic area and volume measurements of what it is that you are seeing. So you can be confident that if you estimate the area of something based on an MR, that that number is quantitatively accurate.

I think the question Dr. Wilkinson brought up is what is it that you are looking at when you see enhancement

or loss of epidural fat? I certainly agree that there isn't any standard at the moment for an MR definition of scar density. I don't know of any data to indicate the reliability of MR predicting scar density. I also don't know of data to predict that density, as noted by the surgeon at reoperation, predicts how that patient's would have been before operation. That obviously would be limited to those patients who would go back under surgery.

It is clear that it would make the surgery more difficult, but whether it actually predicts the severity of nerve root impingement preoperatively, I don't know of data to that. It would be a difficult study to do for the obvious reasons.

One of the questions that has been raised is the difference between the European and the U.S. studies in terms of the scar called on the MR studies. I think there are some potential MR technical differences that could account for that, but they are obvious, and I'm guessing that they would have been addressed in the design of the study, but I'll bring up them anyway.

Changes in the dose or the nature of the contrast material, or the difference in timing between contrast material administration and imaging could give rise to

differences in the apparent amount of scar. Were those standardized during the study?

DR. ROSS: Yes, they were standardized across both the U.S. and European.

DR. HACKNEY: If there were differences in the equipment, that is the contrast, and ways that you achieved on the images, the pulse sequences that were used, whether fat suppression was used, that could also do it; again, standardized?

DR. ROSS: For the U.S. and the European trial, the index images, the axial T1 weighted spin echo images were the same for both the trials. Really the only difference was one of with the U.S. trial coming later, we added a fast spin echo and sagittal, instead of demanding a conventional first and second echo.

DR. HACKNEY: The sagittal wasn't used for the scar scores then?

DR. ROSS: No.

DR. HACKNEY: Okay, so I think that that addresses the issue of whether there is a technical MR difference accounting for this, and there doesn't seem to be. There are real potential reasons that there might actually be differences. One of them they mentioned is whether the

nature of the lesion in the epidural space initially was different in these groups, and consequently, whether the surgery was different.

Another is are there fundamental differences in the patient populations? Looking at the same group in a European study as in the U.S., are there differences in the proclivity to form scar among the different patient populations? There are some suggestions in other parts of the body that scar formation is not homogeneous across all ethnic and racial groups. It is at least conceivable that could be a real difference, not an artifact, not a problem with the study, but an actual, substantial difference between these patients.

The other question of course is whether there are systematic differences in surgical technique between Europe and the United States.

Another issue about the way the MR study was done, I think the inclusion of the posterior quadrants causes a potential problem in interpreting the data. That is, if you want to tell whether ADCON reduces the amount of scar formation, if you include the posterior quadrants, you include another area where ADCON was applied and scar might form.

The assumption though is that it is predominant the anterior quadrants that contain the nerve roots, and those are the ones were you expect scar to correlate with clinical score. If you then defined patients who had extensive anterior scar and little posterior scar, those patients would get scored according to their anterior scar, and you might anticipate a good correlation between scar tissue and clinical outcome.

If you had people who had extensive posterior scar with little anterior scar, they would also get high scores, but those high scores might not correlate at all with their clinical findings, because the nerve root may not be traversing the scar.

I don't know how to solve that problem, short of re-analyzing it, and attempting to determine whether the anterior scars considered alone, and neglecting posterior quadrants would change the results either in terms of the amount of scar that formed, or the relationship between scar formation and clinical outcome.

Finally, the problem that has been raised a lot is you can show that this causes less scar to form in the first place. Whether that actually is beneficial is based on the assumption that the presence of this scar is harmful. One

interpretation of being able to cause a great difference in the amount of scar that forms with a much less dramatic difference in the clinical outcome is that the scar may be an empty phenomenon that is associated with, but not causative of these poorer surgical outcomes.

Perhaps you found a way to break the link between scar and clinical outcome so that you suppress the level of scar formation, but you still have a distribution of clinical outcomes. It may not have been the scar per se that was causing the problem. It's an interesting idea to think about, and I think your study raises a fascinating question.

DR. BOYAN: Thank you very much. Dr. Kerrigan.

DR. KERRIGAN: I have two minor points to add to this discussion. The one, it was curious, somebody mentioned that the reason you didn't see a clinical improvement at 12 months was because of this underlying natural history of the disease, which makes me think, since I'm a rehab doctor, well, why the heck are doing these in the first place? But I don't think we're supposed to be assessing that.

The difference may be between the European results and the U.S. results; perhaps there is a difference in the

underlying disease. Maybe the European patients have a little bit more advanced -- I'm sorry, the other way around -- the U.S. patients may have more advanced disc degeneration, and that's why you see sort of overall increase in scar. Anyway, it just seems to me that might explain some of the reason, not the difference in surgical technique, or in imagine.

The other thing is, after all this I'm really not convinced about the effectiveness. I'm trying to think of anything that would help show was it significant. If you see the scarring on an MRI, well, what does that mean? We really care about with respect to clinically, and I think those nerve roots, that's the key thing. You want a way to assess if there is clinically significant irritation of that nerve root.

That brings me to at least address the issue of putting electrodiagnostic testing an perhaps a function assessment. I know it's not a clean assessment, but you paid the S1 radiculopathy. Doing the H reflex might be helpful and quantifiable in saying how much of a -- is there a reduction in root irritation.

DR. BOYAN: Thank you. Dr. Cheng?

DR. CHENG: As a panel member, we are asked to

discern the safety and effectiveness of your product, and I have just two questions in each realm. First with safety, the product is not intended to be used, and I believe any patients were excluded from your study who had dura tears, is that correct?

DR. SILKAITIS: In terms of both protocol designs for U.S. -- they were to be excluded, but there were inadvertent patients who did have dural tears.

DR. CHENG: Now you realize if the FDA approves this product for your intended use, which is for discectomy at one level, this product will be applied or squirted by surgeons around the world, or at least in the U.S. at multiple levels most likely.

In that case, I look at the complications rate for the European study and note that headache is two and a half times, 4.8 percent, over the control group of 2 percent when your product was used. Do you have any comment about why that was the case?

DR. MC KINLEY: As you know from the report, that was not a statistically significant difference, but I would maybe turn it over to Dr. Hardy, who may have a comment. We don't think it is product-related.

DR. HARDY: Gee, there are so many causes of

headache in a post-operative period. I don't think you can ascribe this necessary to ADCON or lack of its use. I'm not sure you can draw any conclusions.

DR. CHENG: Well, if this product should find its way beneath the dura, are there any studies showing what the harmful effect would be, either animal or human?

DR. SILKAITIS: I would like to maybe talk about some of the patients in the clinical trial. First of all, let me get to the headaches. Some of those were reported four or five months down the road. So they weren't in the immediate post-op period.

We did have two patients that had dural tears in the ADCON-L group. Obviously they got the ADCON-L treatment. What was interesting was that they had virtually no pain at all. They did not have any complaints. When they had their MRI done at six months, it was discovered that they had a pseudomeningocele.

So we have a situation where there were two patients in the ADCON-L group that had dural tears, and basically they were fine. It was only discovered at the six month MRI that there was a pseudomeningocele. They were small in size. They were totally asymptomatic. They didn't know that they had this, and there were no further

treatments for that.

DR. CHENG: Were there any animal studies about the intradural administration of your product?

DR. SILKAITIS: The answer to that question is no, we did not do that.

DR. CHENG: Going on to the second issue, effectiveness of the product. Again, Dr. Janosky raised a critical issue, and that is the reliability. I would like to address by question to Dr. Ross yet again. The kappa or the interobserver variability you quoted was 0.7. That's not the intraobserver variability, or am I misunderstanding you?

DR. ROSS: Yes, between readers, not between myself.

DR. CHENG: So you must have some data on what another reader felt was the presence of scar. In order to get that interobserver variation, you had to ask another radiologist to review these films as well.

DR. ROSS: Correct.

DR. CHENG: So where is that data?

DR. ROSS: That has not been submitted, but that has been submitted to a journal. I mean I have it if you want to look at it, but you have not seen that before. Is

that correct?

DR. SILKAITIS: We submitted the validation report. I think we need to refresh our memories, because it was back in December that it was submitted. We can look for it and respond to you.

DR. CHENG: I am rather surprised that it wouldn't have been submitted, because if it validated the findings of Dr. Ross, it would have strengthened your PMA application significantly. Since the essence of what we are talking about here is a reduction of scar, the impressions of Dr. Ross' radiographic reports are essential to the determination of whether or not your product is successful or not.

DR. SILKAITIS: Yes, we did submit a validation report in the PMA. Just my memory fails me right now as to the actual results of that report; the details of it.

DR. CHENG: Okay. Then since we know the interobservation variation, what about the intraobserver variation?

DR. SILKAITIS: If you can give us a moment, we will look for that report.

DR. CHENG: Okay.

DR. BOYAN: Dr. Bauer, a couple of questions,

after which we will ask the company representatives to step down, and we'll have a discussion on the FDA questions. So you are the last.

DR. BAUER: Just a short question. I wonder if the manufacturer has prepared a concise list of claims?

DR. SILKAITIS: I apologize. We were convening here to try to find the report. Could you repeat the question, please?

DR. BAUER: Have you written out a list of claims?

DR. SILKAITIS: Yes, there was a draft package insert that was initially submitted.

DR. BAUER: I see a package insert, but it's a three or four page thing. Do you have a specific list of claims separate from that?

DR. SILKAITIS: It is under indications. We had it up on the screen when we started the presentation.

MS. NASHMAN: Dr. Bauer, could let us know where you are looking in that panel pack, so the rest of the panel can look as well?

DR. BAUER: My page number is 6580.

DR. SILKAITIS: Now I would like to add one comment to that. That is draft, and we know we have to work on it to beef it up a little bit, because more information

was submitted to the agency.

DR. BAUER: I'll probably reserve further comment on this a little later, but I think that to have the panel focus on those claims, specifically, the indications, can maybe facilitate our discussion a little bit.

Concerning this inter- and intraobserver variability, undoubtedly FDA has had the opportunity to review that data, if we haven't. At least, I haven't spent the time to do it. I wonder if we can ask someone from FDA to comment specifically on inter- versus intraobserver variability?

DR. BOYAN: Could the statistician that reviewed the data for the FDA please come forward?

DR. BUSHAR: I'm the statistician that did the PMA, but I don't remember seeing that, or reviewing that at all. Obviously, it's an extremely important question, but it just sort of slipped. We didn't look at that. We were very happy that there was one radiologist who did both studies, so we were looking for consistency, because we know there is a devil of a difference between radiologists. As far as the validation study, I mean if it's in there, I didn't see it. I didn't review it.

DR. SILKAITIS: This was a double-blind,

controlled, clinical trial. So whatever would happen to the control group, would also be affected in the treatment group.

DR. BOYAN: Dr. Bauer, do you have any other questions?

DR. BAUER: No.

DR. JANOSKY: Excuse me. You answered -- I just asked that question again about reliability. I said, which way were the errors occurring, and it was answered that it was clearly in the non-extensive part. So what were you giving me data from then? Was it intra or inter?

DR. MC KINLEY: It is inter.

DR. JANOSKY: And this is that kappa value that we were talking about before. So I didn't see any intra in the application. Were you able to locate it? For this particular study, that's actually the most important type, given that you only have one rater doing all the assessment.

DR. SILKAITIS: We have to look for it.

DR. WILKINSON: But it wasn't presented.

DR. BOYAN: What I would like to do now, while you are looking, is give one last chance, because I really am going to make you go sit in the audience here. I really am going to do it.

Yes, Dr. Witten?

DR. WITTEN: I just want to make one comment that the panel might want to consider in its deliberations. That is, there has been discussion this afternoon both about clinical benefit, and also about benefit as demonstrated by the radiologic study. Ms. Domescus asked a question about benefit as demonstrated by the radiologic study in particular.

I just want to mention that we have other adhesion barriers that we have approved, not for the spine, on the basis of surrogate endpoints that were thought to be clinically relevant, and have some clinical significance to the difference demonstrated. So that should be considered.

DR. CHENG: Are we supposed to consider this application in comparison to other items which have been approved by the FDA, or on the data of this PMA alone?

DR. WITTEN: No, it should be considered on the data of this PMA alone. I'm just mentioning that surrogate endpoint. If it is felt by the panel to be relevant and a significant benefit demonstrated, could be something the panel could consider.

DR. BOYAN: So I would like to summarize the discussion, and see if that would be helpful. In this I

think we have had a discussion of the MRI technique from an expert who has certainly presented the opinion, at least as I heard it, that the technique used in this study was valid, and certainly indicated that there was a reduction in scar over time, and that that could be quantitated to at least within the limits of the technology at this time.

Is that an accurate assessment of what you said, Dr. Hackney?

DR. HACKNEY: The other thing I would bring up that I meant to mention about the kappa scores is that in radiologic studies when there is interpretation involved, as there is in this one, very high kappa scores aren't seen. There was a nice review of this a few years ago, where they came up with a 0.85 as the functional equivalent of perfect agreement. That's about the highest anyone ever finds in radiologic studies where someone has to make an interpretation, not merely comment on the presence or absence of a large, obvious finding.

The other thing that I point out is that if we are -- my concern about this is that we have much better evidence that it works radiographically than we do that it works clinically. To the extent that they are able to demonstrate a difference based on radiographic studies that

says that whatever the level of reliability was, it was high enough to permit that.

If we are concerned about bias that is selectively favored, calling lower scores on patients treated with ADCON, then I think that we are not looking at reliability issue, we are looking at a bias issue. If this were a highly unreliable measure of scar, then the anticipated result would be no difference, because it would be too imprecise a measure in order to detect the difference.

So I am much less concerned than I think some other people are about the reliability and precision of the MR measurement. What I am concerned about is whether making the MR scan look better in six months is the goal. If the goal is to make the patients look better, it is not so clear that this does that.

DR. BOYAN: Thank you very much. That was an important point.

Then we have two indicators. One is clinical, that the advantage to the patient, both in terms of the speed and the quality of their lives following the first surgery. Then the issue raised by Ms. Domescus, that there is also an advantage in the second surgery. There appears to be an advantage in the second surgery that the surgery

would be less rigorous because of the potential use of this product.

So those are the two issues, clinical effectiveness to the patient immediately following the first surgery, as well as the potential for clinical effectiveness following second surgery.

I think that we have certainly heard a lot of the issues and concerns raised by the panel. I would like to have one opportunity for any member of the panel that would like to ask a very pressing question that they felt was not answered by either the FDA or the company, and then we'll ask the company to step down. Is there anyone else that has any other question that needs to be addressed?

DR. CHENG: I don't think my questions were answered yet by the sponsor.

DR. BOYAN: Okay, repeat your question, because I think they have been looking for your data.

DR. CHENG: Do you have the answer?

DR. SILKAITIS: Could you help us and repeat the specific question you were interested in?

DR. CHENG: It dealt with the intraobserver reliability and validity in that aspect.

DR. YASZEMSKI: Dr. Hackney, could you repeat what

you said was an appropriate radiologic kappa? I just didn't hear you.

DR. HACKNEY: What I was saying was that when you do radiologic studies that look at kappa scores, both inter and intra, and there is an element of interpretation involved, as there is here, you don't get extraordinarily high kappa scores. People disagree with themselves and with one another. A kappa score of about 0.85 is the highest you will see in a study where there is some sort of interpretation involved.

Now if you are talking about does this patient have a lung on the left side or not, then you expect to get extraordinarily high scores, but for interpretation studies, very high kappa scores don't come up, and kappa scores in a 0.7 range, you can certainly get higher than that, but that is not considered a poor reproducibility at all. As I said, I didn't think that was going to be that much of an issue, or I would have brought some of the reference to document that.

One of the things about radiology is that the data you were using is always available to be completely reproduced, and so you see what the level of reproducibility of interpretation is.

DR. WILKINSON: Since the question being asked is for data that was not included in the PMA, are we allowed to review that data? I thought that only data that was available to us prior to this meeting was to be considered.

DR. BOYAN: Are you asking about the data that Dr. Cheng is asking about?

DR. WILKINSON: The intraobserver data that was not made available to our statistician or to us.

DR. BOYAN: My feeling is that it's a significant enough question that it has been raised by several people. If the data is available here at this meeting, we might as well have the answer to it.

DR. MC KINLEY: I found the interobservability report. That is on page 2894 of the PMA.

DR. BOYAN: Thank you. What about the intra?

DR. MC KINLEY: I have not located the intra.

DR. BOYAN: So if these are the facts, that we haven't located it, then I think that we can hunt for it forever.

Then let's go on to the next stage here. Now I suggest that we need a stretch break. Again, I'm hesitant to let anybody out of the room. So the stretch break can take three minutes.

[Brief recess.]

**Agenda Item: Questions and Voting**

DR. BOYAN: We're going to begin this part of this discussion by going through the questions that were asked of us to consider by the FDA. I'm not going to require us to read through these again. These are pretty lengthy questions. Just to simply go to the questions and remind the panel of what the subject matter, then invite each member of the panel to address this.

We'll go around the room. I'll just pick a place to start, so that everybody gets a chance. I probably will select a starting spot based on subject matter.

The first question that they have asked us to address is the MRI technique. So I think it's an appropriate place to start with Dr. Hackney, on Question 1A. Does the company establish the validity of the MRI technique for evaluating the extent of peridural fibrosis?

DR. HACKNEY: I would say yes.

DR. BOYAN: Dr. Hale?

DR. HALE: Based on Dr. Hackney's comments, I would say yes, that they established the validity for establishing the presence. I'm not quite sure how extent is

interpreted, but I would say definitely they established the presence of scar.

DR. BOYAN: Thank you. Dr. Yaszemski?

DR. YASZEMSKI: Yes.

DR. BOYAN: Dr. Janosky?

DR. JANOSKY: I would say no, or tentatively perhaps. I think the issue of reliability, even if we go to standard of a kappa being 0.85, they are getting values much less, and there are clearly ways that you can do to try to up that grade of reliability. So I can't make a claim for validity without saying the issue of reliability has not been addressed satisfactorily.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: I'll say a tentative yes.

DR. BOYAN: Dr. Wilkinson?

DR. WILKINSON: I also would say a tentative yes for extent, but certainly not for density of scar.

DR. BOYAN: Dr. Holeman?

DR. HOLEMAN: I yield to my medical colleagues' decision.

DR. BOYAN: Ms. Domescus?

MS. DOMECUS: I would say yes.

DR. BOYAN: Dr. Bauer?

DR. BAUER: I think that if you take only the data presented by the company, then it would be probable. I think that when you take into consideration other factors, such as previous publications concerning MR and its identification of fibrosis, then I think a reasonable answer is yes.

DR. BOYAN: Thank you. Dr. Cheng?

DR. CHENG: Strictly the way the question is worded, I would say no. I think the use of MRI and the value of it for looking at fibrosis is unquestioned, as Dr. Hackney has already reiterated, but I think the validity, because of the questions raised previously, do not confirm answering this in a yes.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: I would say, with just one little concern left over of the validity with respect to ADCON; whether that interferes with the MRIs.

DR. BOYAN: I would like to now go to the next part of this question. It is a follow-on, so we'll start again with Dr. Hackney. Do the PMA data that we were presented establish that this MRI technique has adequate sensitivity to measure the extent of peridural fibrosis?

DR. HACKNEY: I'm not sure how this question is

meaningfully different than Question A. I don't think the PMA did or tried to establish that. I believe that the accuracy of MR for this purpose, for detecting and characterizing the location of scar is well established. I don't think the PMA really contributed to that. I think they gave evidence that shows that it is good enough for their purpose of this study, is the best I can do of interpreting it.

So the question I think this is asking is, is this a useful technique for what they are planning it for? I would say yes.

DR. BOYAN: Dr. Hale? I think this question also incorporates the information that was in the peer reviewed article that was provided.

DR. HALE: I would say yes.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: I think I'm going to say no, and I'm going to base it on what Dr. Bauer said, that the previous literature makes me answer yes to A, but that the data here today taken by themselves, my answer to B is no.

DR. BOYAN: Dr. Janosky?

DR. JANOSKY: Was it established in the PMA? I would say no.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: In the PMA? No.

DR. WILKINSON: I would agree.

DR. HOLEMAN: No comment.

MS. DOMECUS: I'm not sure whether or not the PMA contained a summary of the clinical literature is helping other panel members say yes to A and no to B, because I wasn't supplied with the entire PMA, but I am comforted.

DR. BOYAN: The PMA did include the article. At least the information that was sent to us did the include the peer reviewed article.

MS. DOMECUS: Then I would say yes to both.

DR. WILKINSON: But it included only that one article, not the other articles that Dr. Hackney referred to.

DR. BOYAN: Yes, Dr. Silkatis?

DR. SILKAITIS: We submitted with the PMA, numerous articles to the FDA. Whether they were part of your panel packet, I'm not sure. We also had references in the PMA to address the MR.

DR. BOYAN: I have to say that I think in the total amount of documentation that we received, that those articles were included. There was boxes and boxes.

MS. DOMECUS: I just want to make the panel members aren't confused, and they are saying it wasn't in the PMA. There is a difference between the whole PMA and the clinical study of just this device. So if they are answering yes to A and no to B, because B doesn't include the clinical literature, the clinical literature was in the PMA, so it can be considered in total.

MS. NASHMAN: I just wanted to point out for the record what was indeed sent. We included a panel pack which included: FDA reviews; correspondence between FDA and the firm; summary of safety and effectiveness; and FDA's description. That was to be used, and panel members were told that this was to be used as a guide in their review. It was all the information hopefully that they could use to get a good idea of what was contained in the I believe 40 pound box of volumes that was sent to them.

The volumes to be sent was discussed between the manufacturer and the FDA. The actual volumes were sent by Gliatech in specific boxes, in individual sets I believe. Perhaps we boxed them, but Gliatech is fully aware of the information that we sent to each panel member. In fact, all the information that we requested from Gliatech, was then transferred to the panel members. So there should be no

uncertainty that the panel members didn't receive all the information that you wished them to see.

DR. BOYAN: I would like to second that.

Dr. Silkaitis?

DR. SILKAITIS: I was just going to add that, yes, there were reprinted included.

DR. BOYAN: Dr. Bauer?

DR. BAUER: In responding to the question, I suppose strictly speaking, maybe not, but I actually thought it was a pretty good article. From a practical standpoint, peridural fibrosis is a reasonable clinical problem. If you are not going to use this method, then what else are you going to use? I think from a practical standpoint, yes.

DR. BOYAN: Dr. Cheng?

DR. CHENG: Yes, I don't think PMA data established this, but that was not the intent of the PMA. I did read Dr. Ross' article. I also thought it was a very good article, and I also agree that MRI technique is the best way of looking at this given the inherent disadvantages that we just discussed today.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: No comment.

DR. BOYAN: Part C of the same question, so we

stay with Dr. Hackney. Can a change in MRI scores of peridural fibrosis in both groups between 6 and 12 months be attributed to clinical changes, or is it possibly due to the MRI technique? I believe you addressed this earlier, but if you would repeat it, that would be great.

DR. HACKNEY: I don't think it is due to a difference in the way the MR images were acquired. It is I suppose possible it could be due to a change in interpretation criteria. It would require again, an assumption of some sort of bias in order for that to be significant issue. I haven't heard any suggestion of that.

As I indicated, I don't find the fact that some MRI scores change between 6 and 12 months to be surprising or problematic. That is the expected outcome if you follow a substantial number of people. So I would say it is most likely attributed to clinical changes, and definitely not to technical issues in the way the MR images were acquired.

DR. BOYAN: Dr. Hale?

DR. HALE: I would agree with Dr. Hackney. It doesn't seem to follow that it would be due to the MRI technique. Whether it is actually clinical changes or something else, I can't comment on that.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: I answer yes.

DR. BOYAN: Dr. Janosky?

DR. JANOSKY: I don't think there is any way to know what it is due to the protocol that was used.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: I agree with Dr. Hackney.

DR. BOYAN: Dr. Wilkinson?

DR. WILKINSON: I was struck that the reduction in extensive scar was 26 percent in the ADCON-L group, and 18 percent in the control group, which seems to me to be more than chance, but I have no way of knowing.

DR. BOYAN: Dr. Holeman didn't have a response at this point. Ms. Domescus?

MS. DOMECUS: I agree with Dr. Hackney.

DR. BOYAN: Dr. Bauer?

DR. BAUER: I don't know.

DR. BOYAN: Dr. Cheng?

DR. CHENG: I don't know either.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: I agree with Dr. Hackney.

DR. BOYAN: Okay, now we've got a new question. First, do we all feel that we have handled this question adequately? How about FDA, do you feel that we have given

you the information you need?

DR. WITTEN: Yes, thank you.

When you read the next question, I would actually, based on the discussion that was had, want to make sure to clarify the question.

DR. BOYAN: Why don't you do that now, because I'm not going to read the whole question. I was just going to address this right down to the bottom line. Do the PMA data demonstrate a clinical benefit? So now to you Dr. Witten.

DR. WITTEN: Okay, that is the part I would like to clarify. I suppose our question could be more clearly stated as, do the PMA data demonstrate a clinical benefit, either measured directly by clinical endpoint or measured by a clinically relevant surrogate?

DR. BOYAN: Did everybody hear that? Why don't begin that with --

DR. JANOSKY: Can you please repeat that?

DR. WITTEN: Do the PMA data demonstrate a clinical benefit, either measured directly by clinical endpoint or measured by a clinically relevant surrogate?

DR. BOYAN: By surrogate, Dr. Witten, give us some examples.

DR. WITTEN: Well, for example, we talked a lot

here about the pain and about radiologic findings. Pain we would consider a directly measured benefit, but then as Ms. Domescus pointed out, then there is the question of whether the radiologic findings could be considered a clinically relevant surrogate as related to something else perhaps.

DR. WILKINSON: Can I ask for further clarification?

DR. BOYAN: Sure.

DR. WILKINSON: Is it sufficient that this be a clinically relative surrogate, or also a reliable surrogate? Because yes, it has relevance, but the relevance may not be significant.

DR. WITTEN: Yes, I shouldn't say just by clinically relevant surrogate, but demonstrated in a manner consistent with good scientific evidence.

DR. BOYAN: I'll take the courageous first step of starting, and then we'll go towards Dr. Yaszemski. I would say that yes, they do. I thought that they demonstrated a clinical benefit certainly in the European study. The U.S. study may too soon to make a final statement, but it seemed clear to me that there was reduction in pain. I'm not knowledgeable enough to know how significant that was, and I would refer that to Dr. Kerrigan or Dr. Cheng, Dr.

Wilkinson.

I do think that the data convinced that there was a clinical benefit in that realm, as well as in the positive effect of the second surgery. That there was a reduction in scar. Biochemically, I understand why it took place. I think that there is a biological foundation to the data that they got, and I'm comfortable with that. I don't think it is phenomenology. I think it is real, so my answer is yes.

Dr. Yaszemski?

DR. YASZEMSKI: I am going to answer yes, and I'm going to invoke one of Dr. Witten's surrogates. I'll say that that surrogate will be the MRI evidence of decrease in peridural fibrosis. The reason I say that is I'm going to submit to all of us that these patients came to the surgeon; got a diagnosis of something that they and the surgeon thought could be treated surgically.

I'll submit that hopefully in a great number of these patients, the decrease in their pain was related to successful choice of a surgical management and effective execution of that surgery, and not solely related to the device, because as we have heard, there is not a clear cut relationship between the persons who have fibrosis post-operatively, and linking pain in a causal fashion to that

fibrosis.

However, I do think it's a good thing to try to decrease that fibrosis, and I think the MRI shows that. I vote yes.

DR. BOYAN: Dr. Janosky.

DR. JANOSKY: I would say yes, but with a very, very low level of confidence in that yes.

DR. LAURENCIN: To make things confusing I would say yes/no. In terms of the primary outcome, in terms of the MRI findings, I think the answer is yes, but in terms of the secondary outcome, in terms of pain relief, my answer would be no. The question is if someone does an operation and you have one day of pain relief, and you do something different with the patient, is that successful?

Everyone would agree no. If it is a week, probably not. A month? Probably not. Six months, a year, I'm not sure, but certainly the effects in terms of using the ADCON, in terms of pain, by all the data they have shown me, really don't carry out to one year. So in terms of being able to say this is something that relieves -- and if you look at their package insert, it says relieves fibrosis in their clinical sequelae, implying that the clinical sequelae of course is pain.

That to me also connotes something that the clinical sequelae being something more of a long term, at least at a one year basis. So for that reason I think that I can't say that it fulfills the secondary outcome.

DR. WILKINSON: I would have to say no. There was no relief of sciatica in the United States or European trial. In the published paper, only one of three categories of type of pain showed correlation. Straight leg raising was improved more on the side opposite to the application than on the side of the application. The wARP data is suspect, and it was positive only in the United States study, and negative in the European study.

The Roland-Morris scale was not convincing as being of any clinical significance. The MRI correlation between the extent and the clinical significance of MRI was not established in the prior literature, or in the present study. Density of scar is probably a much more important clinical phenomenon than extent of scar.

Finally, when patients were reoperated, dorsal scar was actually more firm in those patients at the site of ADCON application.

DR. BOYAN: Dr. Holeman?

DR. HOLEMAN: I will have to say no. It has not

been convincingly shown that there is a correlation between scar formation and the occurrence and/or the severity of pain. For a patient to agree to the insertion of this device with the hope of pain reduction in the future could only be based on a theoretically determined correlation, and not on one that has been pathologically and/or empirically validated.

Based on the discussion this morning, I can only conclude that with or without this device, there may or may not be pain. Data collected on a device that is designed to be clinically beneficial to the patient should clearly yield statistical significance between groups of patients when appropriately assessed.

To place a device on the market with the purpose of satisfactory clinical outcomes for the patient, then the results should clearly show the benefit. To reduce the identification of clinical benefit to a question of statistical significance in my mind, minimizes the importance of the patient, and the resulting quality of life.

MS. DOMECUS: I think the clinical benefit has been demonstrated. I think it is important to understand the different data sets that are put before us, and the

validity of them. The PMA, as I understand, was based on the pivotal European trial, and that was set up to be a six month study, and that data was supportive.

I think that the data points that are troubling to the panel is the 12 month data from the European study, which was not part of the original study design. By the way, that P value is 0.06, which is a comment I made earlier about how close the numbers are; and the six month data in the U.S. study.

Again, the 12 month European time point, and the 6 month U.S. time point, to not have sufficient numbers yet for statistical power, so I don't that the not statistically significant results should be held against the manufacturer at this point.

I also think with regard to Dr. Yaszemski's comments that I agree that a reduction in fibrosis should be considered a surrogate endpoint. There is a significant amount of effort on industry's part to come up with devices that prevent adhesions. I see a lot of effort in the medical community in terms of clinical literature and surgical technique to prevent adhesions.

It was suggested that adhesions are a bad thing, and anything you can do to prevent them is good. Even they

are maybe somewhat -- the strength of the correlations isn't comforting at all time points, I think that it is just intuitive that a reduction of fibrosis is a clinical benefit.

DR. BOYAN: Thank you. Dr. Bauer?

DR. BAUER: I appreciate the comments Dr. Holeman just made. I think those are quite relevant and good observations. Having said that, I still am going to respond yes, essentially echoing the comments of Dr. Yaszemski.

DR. BOYAN: Thank you. Dr. Cheng?

DR. CHENG: Do the PMA establish clinical benefit? Yes, although I think it is quite low.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: I think they probably do not for the reasons I have said before. I don't think that the clinical findings are that significant. The pain doesn't seem although statistically significant, in one part of the study doesn't seem to be really clinically significant. I have an inkling that it could be demonstrated, but the data as they are, I can't say that they do.

DR. BOYAN: Dr. Hackney?

DR. HACKNEY: Since we have a two part question, I'll have a two part answer. I think clinically the

clinical advantage that they have actually demonstrated I would consider marginal at best, and I would answer no to that part of it. Clinically relevant surrogate, a weak yes. I think they clearly demonstrated a difference.

The question is, how relevant is this MR difference that they have been able to demonstrate? If we say yes to this question, we would be hoping that the MR difference is really the truth, and that for some reason we have underestimated the clinical difference in this study, and perhaps if we had a much larger group of patients, the clinical results would track the MR results, but at the moment we have good MR results, and very weak clinical results.

Unless our goal is to make the MR image look better, and the surgeons have raised the possibility that maybe simply reducing scar isn't in and of itself good, even if we can't prove the clinical utility here, so I would give it a weak yes for clinically relevant surrogate, and a no for current clinical direct measures.

DR. BOYAN: Dr. Hale?

DR. HALE: I would answer yes, based primarily on the MR findings, and also the data related to the reoperation group. With regards to the secondary outcome

criterion, particularly the pain scores as 12 months, those are certainly less convincing.

DR. BOYAN: Thank you. We have an opportunity here to ask FDA if we have answered that question sufficiently?

DR. WITTEN: Yes, thank you.

DR. BOYAN: Okay, we're on to the label. So everybody has a draft of the label in their panel pack. The question here is can the PMA data be extrapolated to include a generalized use for lumbar surgical procedures?

Let's start that one with you, Dr. Laurencin.

DR. LAURENCIN: I would say no, and the reason is that I don't see enough information regarding the effects on the dural or the sequelae after a dural tear.

DR. BOYAN: Dr. Wilkinson?

DR. WILKINSON: I would say no. A spinal procedure that does not reach the dura, would not be affected by this product.

DR. BOYAN: Dr. Holeman?

DR. HOLEMAN: I yield to a medical decision.

DR. BOYAN: Ms. Domecus?

MS. DOMECUS: I echo the consumer representative's comments.

DR. BOYAN: Dr. Bauer?

DR. BAUER: Lumbar surgical procedures is too vague, and I would suggest that it be altered to reflect those procedures that were used in the study.

DR. BOYAN: Dr. Cheng?

DR. CHENG: I am wondering what lumbar surgical procedures is the FDA asking about?

DR. BOYAN: Could we have clarification from the FDA?

DR. WITTEN: Our question is reflective of what labeling is requested by the sponsor. The sponsor is requesting this indication for use during lumbar surgical procedures. So what we would like is some help from you all in clarifying how specific that needs to be.

DR. BOYAN: You want us to provide you some limitations or some guidance. So I think that Dr. Bauer has given some guidance. Dr. Cheng, that's the goal.

DR. CHENG: Well, then I would probably modify that to insure that this is in the absence of intradural exposure, and for application when there has been decompression or discectomy.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: It's beyond my expertise.

DR. BOYAN: Dr. Hackney?

DR. HACKNEY: I defer to the surgeons.

DR. BOYAN: Dr. Hale?

DR. HALE: I'm not sure that I can directly answer this either, but Dr. Wilkinson raised a concern earlier that would affect my consideration of this, and that was that he questioned or implied that the results of the surgery were dependent on the amount of bone that was removed, or there was some question as to whether that was the case. That seems to be directly relevant to this question.

DR. BOYAN: Dr. Wilkinson?

DR. WILKINSON: Well, I think the point I would make in response to this question is that the device is intended only for epidural use. So spinal procedures that are done inside the dura shouldn't be applicable. Procedures like a posterior fusion with pedigal(?) screws, where the dura is never exposed, this device would have no applicability.

So if you expose the dura and keep the dura intact, that is what was studied. All these other things weren't studied. It is probably unsafe to put it in the subarachnoid space, which is clearly a lumbar surgical procedure. It's probably unnecessary to put it outside the

pedigals.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: I'm going to vote no for the reasons that have been brought up, and one other concern that I will mention. That is when reviewing the data that was given to us, all the data is for one level procedures. If it is extrapolated, and as an example, if someone did a procedure where they exposed the dura from L1 to S1, and then covered the entire length, we might perhaps experience an unknown sequela of that based upon the volume of material that would be put over that extent.

I would like to see some data that includes higher volumes of the material over several levels before I would be comfortable saying that. As an example in other resorbable materials, occasionally when the size of the device gets very large, depending upon the nature of the biodegradation, and when the mass load is released, some local tissue problems occur.

So I think I would stick to the data that was presented, which is one level data.

DR. BOYAN: Thank you. Dr. Janosky?

DR. JANOSKY: I'll defer.

DR. BOYAN: Any other comments on the labeling?

DR. WITTEN: That's what I was just going to ask, if there were any other comments on the labeling.

DR. BOYAN: I think that there may be some just -- Dr. Hackney?

DR. HACKNEY: I think it was raised before that the labeling doesn't really address the issue of clinical efficacy of this. I think that somewhere in there, the largely negative clinical outcome associated with this product should be indicated in the label.

DR. BOYAN: There are a few minor things. One thing we might do is provide -- if we have specific wording issues or other things, provide that to Ms. Nashman, and she can then convey it to the FDA.

I would like to state though that from my point of view, as people are becoming more and more sophisticated, that I would like to see a greater detail than polyglycan ester. I think this is a specific polyglycan ester, and its strength is that it is sulfated, that is not a neutral one. I wouldn't want to have a situation arise where someone might become confused as to what you are putting there. So I would clearly state what the components are.

The other thing that hit me as I looked at the adverse events is when I compare controls to ADCON-L, for

reasons that aren't clear to me, the order of the first two adverse events has been switched, and it makes me, the reader wonder if I had a patient that I was more worried about a sensory deficit with, I would give them ADCON-L, and if I had a patient that I was more worried about a motor deficit with, I would give them the control.

Maybe that's not what you intended. Maybe that is a typo. So you might want to look at your label really closely.

Any other comments?

DR. WILKINSON: I might just comment that I certainly agree with Dr. Yaszemski that there may be quite significantly different toxicities if the material is applied over a very large extent of exposed dura, as opposed to a limited extent.

DR. BOYAN: All right, so this section is brought to a close. Now, one last thing before we get to the voting in a moment. Any issues that are rankling that need to be dealt with? Any last minute discussion items that need to be discussed?

See none, I'm going to turn the table back over to Ms. Nashman, who is going to read us our instructions.

MS. NASHMAN: Panel recommendation options for

pre-market approval applications. The medical device amendments to the federal Food, Drug, and Cosmetic Act require that the Food and Drug Administration obtain a recommendation from an outside expert advisory panel on designated medical device pre-market approval applications that are filed with agency.

The PMA must stand on its own merits, and the recommendation must be supported by safety and effectiveness data in the application, or by applicable, publicly available information. Safety is defined in the act as reasonable assurance based on valid scientific evidence that the probable benefits to health under conditions of use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses and conditions of use when labeled will provide clinically significant results.

Your recommendation options for the vote are as follows:

1. Approval. There are no conditions attached.

2. Approvable with conditions. You may recommend that the PMA be found approvable subject to specified conditions such as resolution of clearly identified

deficiencies which have been cited by your or by FDA staff. Prior to voting, all the conditions are discussed by the panel and listed by the panel chair.

You may specify what type of follow-up to the applicant's response to the conditions of your approval recommendation you want, for example, FDA or panel. Panel follow-up is usually done through homework assignments to the primary reviewers of the application, or to other specified members of the panel. A formal discussion of the application at a future panel meeting is not usually held.

If you recommend post-approval requirements to be imposed as a condition of approval, then your recommendation should address the following points: (a) the purpose of the requirement; (b) the number of subjects to be evaluated; and (c) the reports that should be required to be submitted.

3. Not approvable. Of the five reasons the act specifies for denial of approval, the following three reasons are applicable to panel deliberations: (a) the data do not provide reasonable assurance that the device is safe under the conditions of use prescribed, recommended, or suggested in the proposed labeling; (b) reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in

the labeling; and (c) based on a fair evaluation of the all material facts in your discussions, you believe the proposed labeling to be false and misleading.

If you recommend that the application is not approvable for any of these stated reasons, then we ask you to identify the measures you think are necessary for the application to be place in an approvable form.

It is noted that following the voting, the chair will ask each panel member to present a brief statement outlining the reasons for their vote. Traditionally, the consumer representative and the industry representative do not vote, and Dr. Boyan as chairperson votes only in the case of a tie.

Dr. Boyan.

DR. BOYAN: Thank you. Before the beginning of the voting process, I would like to mention for both the panel's benefit and for the record, the votes taken are votes in favor of or against the motion made by the panel. Votes are not for or against a product.

I would ask Dr. Bauer if you would like to lead with the motion?

DR. BAUER: Thank you. I would like to move approval pending resolution of only a few minor points.

Those points again relate to what I interpret essentially as claims as are listed on the package insert.

We have talked already about the statement in paragraph three that currently reads, "ADCON-L anti-adhesion barrier gel is indicated for use during lumbar surgical procedures, providing a temporary physical barrier to inhibit post-surgical peridural fibrosis and adhesions, and their resultant clinical sequelae."

There are several parts to this statement. The first relates to the "lumbar surgical procedures." I would suggest that FDA and Gliatech work together to come up with wording that appropriately reflects the procedures that were studied in the PMA.

Secondly, reflecting Dr. Laurencin's comments earlier, I would suggest that Gliatech work with FDA to come up with mutually agreeable wording concerning the phrase, "the resultant sequelae."

Finally, on the last paragraph of that first column, I would truncate that paragraph simply to read, "As with any resorbable, implantable medical device a transient foreign body reaction may occur."

That's all.

DR. BOYAN: Okay, let me see if I can repeat back

what you just said. You are moving approval with conditions that FDA and Gliatech are to work together to find appropriate wording which would reflect the actual procedures done, the actual sequelae, and the -- I forget the word for it. I'll come up with it in a second, but it has to do with foreign body reaction, as well as appropriate changes to the labeling. Would you add that?

DR. BAUER: Yes.

DR. BOYAN: Okay. Is there a second to that motion?

DR. HACKNEY: Second.

DR. BOYAN: A second from Dr. Hackney. We have a motion on the floor, and we can now have discussion of the motion. Comments? Any discussion?

DR. LAURENCIN: I would propose just a small amendment to the motion. That is the fact that perhaps there should be a line that states that long term clinical benefit in terms of pain relief with use of the ADCON has not been demonstrated.

DR. BOYAN: Is that an acceptable amendment to you, Dr. Bauer?

DR. BAUER: Yes.

DR. WILKINSON: Second the amendment.

DR. BOYAN: Any other comments that we need?

DR. YASZEMSKI: I'd like to suggest we are discussing the label, and with respect to the label I would like to suggest as I did before, that it be modified to reflect single level application, and that the effectiveness statement, rather than saying the resultant clinical sequelae of peridural fibrosis, simply state that the data have shown a decrease in peridural fibrosis.

I think, going along with Dr. Boyan's recommendation, I would like to see the IAPAC(?) chemical name for the polyglycan used.

I have one comment not related to the package insert. We have discussed before from Dr. Cheng's and Dr. Janosky's comments about the intraobserver reliability. I would like to ask the sponsor to present that material to FDA for evaluation. That's all.

DR. BOYAN: Is there a second to that amendment?

[The motion is duly seconded.]

DR. BOYAN: Is that amendment acceptable to you, Dr. Bauer?

DR. BAUER: Yes, it is.

DR. BOYAN: Any other amendments?

DR. CHENG: I would like to add an amendment.

DR. BOYAN: Yes, Dr. Cheng?

DR. CHENG: I think the motion would be more acceptable to me if the following amendment was made. I guess I would like to see the FDA have a little less wiggle worm in terms of their wording. For the indications, I would specifically list what this study looked at, and that was one level discectomy.

I would like to see all claims for pain relief removed, and therefore no further comment is probably required, or a comment inserted as Dr. Yaszemski just indicated.

In the contraindications paragraph for the label, I would indicate that subarachnoid exposure is a contraindication to use of the device, because we have no known facts about the safety and efficacy in that situation.

In addition, the last amendment I would like to add is that in the label under the clinical investigation portion where the sponsor describes the double-blind, controlled, clinical investigation that was performed, I would actually list the data from the European study. It's just a small table. We have it in our packets as Table 1, where the percent of scar over 6 and 12 months is identified with the statistical significance.

I would also add a sentence clarifying that, which may be a benefit to surgeons considering use of this device. The statement would read, "Although substantial peridural fibrosis occurred in both groups, there was a slight benefit in the ADCON-L group upon statistical analysis." So that may put this in a better context for the surgeon to consider use of this device.

DR. BOYAN: Is there a second for that amendment?

DR. WILKINSON: Second.

DR. BOYAN: A second by Wilkinson. Is that one acceptable to you, Dr. Bauer?

DR. BAUER: That's getting pretty complicated.

DR. BOYAN: This is going to be impossible for me to read back to you all. I hope you are remembering it as we go along. Are you writing it all down? Good.

DR. BAUER: Could the points be summarized before we vote on it?

DR. BOYAN: You want them summarized before you agree to accept the amendment?

DR. BAUER: Yes, I would.

DR. BOYAN: Okay. Approval with conditions that FDA and Gliatech work together to find appropriate wording that reflects the actual procedures that were done; the list

the expected sequelae; and that --

MS. NASHMAN: Are we still working with removing the result of clinical sequelae or are we changing that to a decrease in peridural fibrosis?

DR. LAURENCIN: I think the amendment was to remove that.

DR. BOYAN: That's right, and we're going to decrease peridural fibrosis, but then we have an adjustment to that from Dr. Cheng, which is --

MS. NASHMAN: Dr. Cheng, help us out there.

DR. BOYAN: Wait, we're not to Dr. Cheng's stuff yet. We're changing that to decrease in peridural fibrosis. Then we are going to make appropriate changes to the labeling. The claims now are going to be specific to a one level discectomy. All claims for pain relief will be removed. The contraindication will be included, and I started off with subarachnoid, and then you had the whole phrase for the condition which I missed the ending, but it's the condition of the inflammation.

DR. BAUER: It's in the tape.

DR. BOYAN: All right, it's in the tape; that it be included as a contraindication. It should also list in the label, the data of the European study as a table, and

there should be a sentence that clarifies that although there was substantial peridural reduction in fibrosis, and then Dr. Cheng, you need to finish, because I got cut off.

DR. CHENG: I stated that although there was substantial peridural fibrosis associated with both treatment groups, there was a slight benefit in the ADCON-L treated group upon statistical analysis. That is with reference to the peridural fibrosis as indicated by the data which is presented in the table, which I requested insertion in the labeling.

DR. BOYAN: So Dr. Cheng's benefit would in effect negate the prior amendment on long term clinical benefit in terms of pain relief.

DR. LAURENCIN: No, I'd like to have that there too, and the fact that the clinical benefit, long term pain relief has actually not been established.

DR. BAUER: Well, I have mixed feelings about this pain business, because I think there is some evidence of pain relief six months. Again, I'm not exactly sure what the best wording for that is, but I don't think that I'm comfortable necessarily precluding that from being included. I think again, that is something that FDA could probably work out.

DR. LAURENCIN: Let me just say from my experience in terms of orthopaedic devices and in terms of having orthopaedic devices sold to me on a daily basis with people coming, with vendors, the worry I have is that a new material that is an anti-adhesion material, anti-fibrosis material will sold not by the people here, not by the people who are making it, but through vendors as a pain relief type of material.

I think that somehow there has to be some information that lets the surgeon know that long term, there are no studies that say long term this is going to --

DR. BAUER: I agree completely with your comments about long term. I'm talking specifically about the six months.

DR. BOYAN: Dr. Kerrigan, did you want to add something to the discussion?

DR. KERRIGAN: I don't think it's been demonstrated. Maybe some of us feel it has been demonstrated; some of us feel it hasn't, but I really don't think it was demonstrated. We might think that it could. Maybe with a really large end we would see some pain relief, but I don't think you can put something on the label if it hasn't been demonstrated, because that's what you are

telling the patient.

DR. WILKINSON: I entirely agree with Dr. Kerrigan that the one demonstration of pain relief is in the wARP score. That was only at six months in the European study, and was not reproduced in the U.S. study. I see no convincing proof of pain relief.

DR. BOYAN: I think Dr. Bauer, that we've got a good claim that there is a reduction in peridural fibrosis. Maybe we should go with the flow here.

DR. YASZEMSKI: I have a quick point of clarification. I heard my recommendation for single level get translated into a recommendation for discectomy only. I feel I would make it somewhat more general, and say single level posterior lumbar laminectomy, as it was presented in the data, which can be single level posterior lumbar surgery, which can be a discectomy or other posterior procedure.

DR. CHENG: Yes, I made that amendment. I would agree with that.

DR. LAURENCIN: I think that what Dr. Bauer is saying is that you agree that some wording saying that long term clinical benefit in terms of pain has not been demonstrated. Your question is whether there should be even

something that says there is data to suggest that there is a six month benefit. You're saying that that probably shouldn't be in?

DR. BAUER: That's correct.

DR. BOYAN: It could be qualified that there may be. If it is qualified, perhaps it would satisfy both physicians.

DR. BAUER: I think that is basically correct. I think that some wording could be worked out that would allow a window of saying something related to pain relief that can be supported statistically at the six month window.

DR. CHENG: What would you suggest, Dr. Bauer?

DR. BAUER: Well, I think that the activity-related pain is, although you obviously disagree with me, I think that in this study, the manufacturer's claim at the P 0.026 level is reasonable, as stated in the last page of their labeling recommendations.

DR. BOYAN: What do you think?

DR. CHENG: I would be more comfortable with Dr. Laurencin's statement. As an orthopaedic surgeon I deal with the vendors and representatives all the time. They are going to be in every doctor's office stating this device relieves pain.

DR. WILKINSON: As a point of order, it is possible to vote on the amendment first, and then the motion.

DR. BOYAN: To vote on the amendment? That's true. That's exactly true. We don't have to have Dr. Bauer have a friendly acceptance of the amendment. There is not going to be a friendly acceptance of that amendment.

DR. BAUER: Perhaps we should vote on that amendment.

DR. BOYAN: Let's vote on the amendment. So we have an amendment. The amendment on the floor, if I can state it correctly, is to remove all claims for pain relief, but to include a sentence that says that long term clinical benefit in terms of pain relief has not been shown. That is the total amendment. So there would be no statement that there could possibly be any relief, and there is a clear statement that long term benefit of relief of pain has not been shown.

We have that amendment. We had a second to the amendment too, didn't we? So now we can vote.

DR. LAURENCIN: That amendment also includes wording regarding one level?

DR. BAUER: That's a separate amendment.

DR. BOYAN: That one has already been accepted I think. It has already been made, fixed, moved around, accepted by the original motion maker. So this is just the pain amendment. All in flavor of the amendment, raise your right hand.

MS. NASHMAN: I'm sorry, you can't do that. For the record, everybody needs to state how they are voting.

DR. BOYAN: You're right, it has to be oral. So let's begin with you Dr. Wilkinson.

DR. WILKINSON: I vote to approve this amendment, that is, deleting claims for pain relief.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: Yes.

DR. BOYAN: Dr. Janosky?

DR. JANOSKY: I agree with the amendment.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: Yes.

DR. BOYAN: Dr. Hale?

DR. HALE: No.

DR. BOYAN: Dr. Hackney?

DR. HACKNEY: Yes.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: Yes.

DR. BOYAN: Dr. Cheng?

DR. CHENG: Yes.

DR. BOYAN: Dr. Bauer?

DR. BAUER: No.

DR. BOYAN: So we have two that are voting against the amendment, and seven that are voting for the amendment. So the amendment carries.

[Whereupon the amendment was approved in a vote of 7 for/2 against.]

Now we have a motion on the floor that has all those parts to it, plus this new amendment, and we have a second. Are there any other changes or suggestions that we would like to articulate before we have a final attempt to read the motion?

Hearing none --

DR. CHENG: I would like to bring one other item up for discussion.

DR. BOYAN: Yes?

DR. CHENG: That relates to Dr. Wilkinson's comment about comparison to fat graft. I don't have a strong feeling one way or the other. There is no claim made for it being better than a fat graft, however, perhaps there should be some wording in there in regards that there is no

benefit in comparison to a fat graft either. I don't know how the rest of the panel feels about that.

DR. BOYAN: So at this point you are proposing that there be a statement included that makes some comment about there has no --

DR. CHENG: I have not proposed an amendment. I would like the panelists' feeling about that; specifically the surgeons.

DR. YASZEMSKI: I would respectfully state that it would be okay to leave it as it is. I think I, as a practicing spine surgeon, when I read that, I would draw my own conclusions about the absence of a comparison.

DR. LAURENCIN: I agree.

DR. WILKINSON: I don't think it needs to be in the device labeling, but it certainly needs to be in the summary of safety and effectiveness that this material was not tested against fat grafting, even though the manufacturer declares that to be the current standard.

DR. BOYAN: FDA, did you hear us on that one?

A motion on the floor ready to vote. Do you want to read through it one more time? I'm going to have Ms. Nashman read through it.

MS. NASHMAN: If we have butchered any portion of

your amendment, please pipe up, because I'm going to be reading, and not looking for your hands.

The motion on the floor is to suggest conditions of approval based on the following condition, which is a rather lengthy amendment to the package insert, which is going to specify the lumbar surgeries which can be performed; specify that there is a decrease in peridural fibrosis; specify the potential for a foreign body reaction. That was the initial amendment as stated by Dr. Bauer.

It was then amended further by the panel that long term clinical benefit of pain relief has not been demonstrated, and therefore all pain claims should be removed.

You need to reflect single level posterior lumbar surgery is what this device is indicated for.

Include the full chemical name within the package insert.

This is outside of the package claim, that the --

DR. WILKINSON: I think it was single level posterior disc surgery.

DR. YASZEMSKI: I didn't say fusion, but what was presented, my reading of the PMA was that it was laminectomies and hemilaminectomies, laminotomies, and

hemilaminotomies. That is what I meant by posterior lumbar surgery, but I certainly did not mean fusion surgery, but I did mean more than simply disc excisions, because a laminotomy or a laminectomy could be done for other reasons.

DR. WILKINSON: So single level laminectomy or laminotomy?

DR. YASZEMSKI: Yes.

DR. BOYAN: Let the tape so reflect that clarification.

MS. NASHMAN: So that was just changed to reflect a single level of posterior laminectomy or laminotomy surgery. This is out of the context of the package insert. You would like the sponsor to present the intrasobserver data. Back to the package insert, contraindicate subarachnoid exposure, and include Dr. Cheng's statement -- and Dr. Cheng, please pay particular attention, because I'm not sure if I caught this -- although substantial peridural fibrosis has occurred, there is a slight statistical benefit for the use of ADCON-L device. Then reference the data. I'm not quite sure which data you are referencing.

DR. CHENG: The data I'm referencing is the actual hard data from the European study, submitted as Table 1 in the handouts which the FDA supplied to us today.

DR. BOYAN: Which should be included in the package insert?

DR. CHENG: The comment which I made, I will repeat it again, although substantial peridural fibrosis occurred in both treatment groups, or perhaps I should say in both experimental groups, there was a slight benefit in the ADCON-L group only upon statistical analysis.

MS. NASHMAN: Thank you.

DR. BOYAN: All right, let's begin the vote. We'll begin with the maker of the motion, Dr. Bauer.

DR. BAUER: I vote yes.

DR. BOYAN: Dr. Cheng?

DR. CHENG: I would vote yes.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: I vote yes.

DR. BOYAN: Dr. Hackney?

DR. HACKNEY: Yes.

DR. BOYAN: Dr. Hale?

DR. HALE: Yes.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: Yes.

DR. BOYAN: Dr. Janosky?

DR. JANOSKY: Yes.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: Yes.

DR. BOYAN: Dr. Wilkinson?

DR. WILKINSON: No.

DR. BOYAN: That's it. So the motion carries. We have one vote against and eight votes for.

[Whereupon the motion was approved by a vote of 8 for/1 against.]

Now let's go back around the room and get the comments as to why you voted the way you did.

Dr. Bauer?

DR. BAUER: This was a large, randomized study with a lot of patients, trying to measure what anatomically is a fairly subtle change, but can be responsible for significant patient morbidity. I think this is difficult to measure, and the measurement thereof has been one of the things we have been struggling with.

I don't think this is a new miracle drug. It is not a new penicillin, but I think it is reasonably safe and efficacious for the uses we have described.

DR. BOYAN: Dr. Cheng?

DR. CHENG: I think that summarizes my feelings as well.

DR. BOYAN: Dr. Kerrigan?

DR. KERRIGAN: I don't have anything to say.

DR. BOYAN: Dr. Hackney?

DR. HACKNEY: I think it is safe, and hope that with much larger studies, the value that they showed on MR will be expressed in clinical value as well.

DR. BOYAN: Dr. Hale?

DR. HALE: I think the data that was presented showed this to be a safe device, and that there is a clinical benefit, however marginal that might be.

DR. BOYAN: Dr. Yaszemski?

DR. YASZEMSKI: The data demonstrated safety to my satisfaction. I think that again, the relationship between the presence of fibrosis and the occurrence of post-surgical pain is certainly not one-to-one, but I think that it is showing that the product did demonstrate a decreased net fibrosis as a step in the right direction, and that I think is adequate efficacy for this purpose.

DR. BOYAN: Dr. Janosky?

DR. JANOSKY: Nothing to new add.

DR. BOYAN: Dr. Laurencin?

DR. LAURENCIN: I do think it is safe efficacy-wise. It's real efficacy at this point may be just in the

fact of reducing scar and making revision surgery a bit easier. Hopefully if the study continues, perhaps the package insert could be changed over the years as they get more data.

DR. BOYAN: Dr. Wilkinson?

DR. WILKINSON: I must say that the emasculated wording is much attractive to me than the original wording, however, I'm still not convinced that there is any clinical significance to the MRI findings that were demonstrated. I would like to say that having been here as a clinician, having tried to do clinical work, I recognize it is much easier to criticize the work of others than to do good clinical studies. I hope these investigators keep working.

DR. BOYAN: Thank you very much. We have some last minute instructions from Ms. Nashman.

MS. NASHMAN: Thank you, I'll be very brief. I would like to take a moment and thank all of the panel members, especially in light of the very long day we had yesterday, and the complex material that we looked at on both days.

I need to go through some procedural points describing what to do with all the information that you have in front of you, and information that you probably have in

your offices in boxes.

I have included in a blue folder either today or yesterday Federal Express labels. You can FedEx the material back to me. There is a sheet also that you need to include, which references the document mail center, which tells them to destroy the material, and not to ship it back to my office. I don't want to see it anymore either.

Third, it's also an option for you to leave all the material that you have here, you can leave it here. You can leave it right at your desk. Please put your name tag on top of it. Or you can deposit it behind you. There is a stack of things going.

Also in the blue folder I have a certification statement, where you will sign a statement stating that you have either personally destroyed your information, or you have returned it to me either at the meeting or back at the office. I need that information faxed to me or mailed to me. We need to use that for our counting.

That is the end of my little procedural things.

Dr. Bauer?

DR. BAUER: So can we shred it ourselves?

MS. NASHMAN: You may shred it yourself and just send me the certification, whichever is easiest for you.

Dr. Witten, do you have any closing remarks?

DR. WITTEN: I just want to thank everyone. I know I shouldn't thank them at length at this point. I would like to thank everyone for participating, the panel, the audience, and the sponsor as well.

[Whereupon the meeting was adjourned at 2:41 p.m.]